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Boeck's Sarcoid (Sarcoidosis). WARFIELD T. LONGCOPE AND J. WILLIAM PIERSON 223

The Use of Para-amino-benzine-sulphonamide or its Derivatives in the Treatment of Beta Haemolytic Streptococcal Meningitis. FRANCIS F. SCHWENTKER, M.D., FREEMAN P. CLASON, M.D., WILLIAM A. MORGAN, M.D., JANVIER W. LINDSAY, M.D., AND PERRIN H. LONG, M.D. 297

Book Reviews 307

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BOECK'S SARCOID (SARCOIDOSIS)

WARFIELD T. LONGCOPE AND J. WILLIAM PIERSON

From the Departments of Medicine and Roentgenology, the Johns Hopkins University and Hospital

Submitted for publication November 20, 1936

The disease variously designated as "Lupus pernio" (Besnier), "Sarcoid" (Boeck), "Benignes miliar lupoid" (Boeck), "Boeck's sarcoid," Benign lymphogranulomatosis (Schaumann); ostitis tuberculosa multiplex cystoides (Jüngling), "Maladie de Besnier-Boeck," and "Hutchinson-Boeck's disease" has been described in one or another of its different phases for many years.

Our information about the condition has accumulated in a most disjointed manner, for it has been referred to quite separately as a disease of the skin, as an affection of the bones, and as a disease of the lymph nodes. It is only within comparatively recent years that these clinical manifestations have been recognized as different expressions of a single pathological process, the etiology of which still remains undetermined. Hunter (1) has published an historical account of the early contributions to the subject. He finds that Jonathan Hutchinson observed a patient with the cutaneous lesions of sarcoid, together with a brawny oedematous swelling of the forefinger, as early as 1869, and described the case with illustrations in 1875. Besnier (2), in 1889, gave a more elaborate account of a patient with large violaceous swellings of the nose, ears, and over the interphalangeal joints of the fingers. He remarked upon the absence of ulceration, the enlargement of cubital lymph nodes and upon the longitudinal striation of the fingernails. He considered the condition different from that described by Hutchinson and called it "Lupus pernio." There are subsequent records of cases published by Tenneson (3) (1892), and again by Hutchinson (4) in 1898, who called the condition after the name of his patient, "Mortimer's Malady." Finally, in 1899, Boeck (5) reported a case somewhat similar to "Mortimer's Malady" with lesions of the skin and pronounced enlargement of the cubital, femoral and axillary

lymph nodes. He studied the histological changes in the skin and since he believed that they resembled sarcoma, he called the condition "Multiple Benign Sarcoid of the Skin." In subsequent publications Boeck (6) gave the results of his clinical studies and histological examinations of the lesions of several more cases, noted that the disease may affect the lymph nodes, mucous membranes and internal organs, recognized the bone lesions that had been previously described, revised his opinion as to its nature, and finally considered it an infectious process nearly related to tuberculosis and possibly due to the tubercle bacillus. He therefore called the condition "Benignes Miliar-Lupoid." Kienbock (7) is credited with the first description in 1902 of the radiological changes occurring in the bones of the hands and feet, though he was ignorant of their relation to sarcoid of the skin, and included his patient in a series of cases of syphilis of the bones. Kreibech (8), in 1904, definitely associated similar lesions in the bones with "Lupus pernio." Much later Jüngling (9), in 1920, described anew these peculiar alterations in the bones which he had first observed in 1911 in a boy, sixteen years of age. He also mentioned three other cases without giving details. At this time, though he was aware that somewhat similar radiological changes had been observed in patients with "Lupus pernio," he concluded, from a histological study of the tissues from the finger, that the process was a peculiar form of tuberculosis, and therefore designated the disease "Ostitis tuberculosa multiplex cystica." Later he (10) recognized the close association which existed between this peculiar disease of the bones and both Boeck's sarcoid and "Lupus pernio." In an excellent article he gave a complete description with many illustrations of the radiological alterations in the bones, and pointed out the peculiar fact that the periosteum and joints were spared in a process that caused extensive alteration in the medullary portions of the phalanges. He studied the histological changes, referred to them as tuberculoid reactions, and was further confirmed in his opinion that the disease was a peculiar form of tuberculosis.

Enlargement of the lymph nodes in connection with sarcoid and "Lupus pernio" had been frequently referred to before Bezancon and Labbé (11), in 1911, described briefly and pictured accurately what they considered to be a particular form of tuberculous adenitis which

seems to correspond closely to the changes now recognized as characteristic of sarcoid. They did not state that lesions of the skin or bones occurred in their patients.

Kuznitzky and Bittorf (12), as early as 1915, regarded Boeck's sarcoid as a generalized disease, possibly of specific nature, and recorded a case in which the lungs were definitely affected. Their patient presented miliary lesions in the skin, enlargement of the lymph nodes, spleen and liver, and involvement of the roots of the lungs with fairly dense shadows extending towards the periphery. They did not regard the disease as tuberculosis, but alluded to it as a generalized disease of unknown etiology.

Since these early publications on the subject, a voluminous literature has accumulated upon "Lupus pernio," Boeck's sarcoid, the related lesions in the internal organs and the etiology of the disease. A full discussion of the lesions of the skin with extensive bibliography is to be found in Volk's (13) article. In the publications of Schaumann (14), Martenstein (15), Goeckerman (16), Kissmeyer (17), Bergel and Scharff (18), and Pautrier (19) there are reports of cases with clinical discussions, descriptions of the pathological lesions and controversial statements concerning the etiology of the disease. In 1934 one entire session of the *Réunion Dermatologique* (20) at Strasbourg was devoted to papers and discussions upon "Sarcoid." The clinical features, the pathology, bone lesions and etiology were discussed.

The disease is usually described as presenting the clinical features of a chronic infectious granuloma, persisting often for years, sometimes spreading slowly from one organ or tissue of the body to another, frequently relapsing, seldom producing serious constitutional symptoms, resistant to treatment, but at times healing spontaneously. Many cases have been reported from Scandinavia, but the disease is known throughout Europe and a number of instances have been recognized in this country (1, 16, 21, 22, 23, 24).

Boeck's sarcoid starts in early adult life. At least half of 200 patients (Kissmeyer (17)) contracted the disease before the age of 30. The progress is insidious until the disease produces obvious changes, most often in the skin, in the lymph nodes, in the bones of the hands and feet or in the lungs. In a few instances the earliest pronounced symptoms have been referable to an involvement of the lungs.

Since the disease is most familiar to the dermatologists, the vast majority of cases have been reported as examples of an eruption of the skin, affecting usually the face, the ears, the nose and the extremities. Boeck originally described three forms: the first typified by small disseminated nodules in the skin; the second by large cutaneous nodosities and the third by infiltrations. These eruptions form firm red, violaceous or brownish swellings, usually well demarcated from the surrounding skin.

Involvement of other organs and tissues of the body takes place regularly in association with the lesions of the skin, and emphasis has frequently been placed upon the fact that sarcoid is a generalized granuloma often occurring as a widely disseminated disease without involvement of the skin.

The lymph nodes are very frequently enlarged, sometimes to a considerable degree. This enlargement may be generalized, as occurred in many of the cases to be reported, or it may be more pronounced in some regions or even limited to groups of nodes, such as the inguinal and femoral, the epitrochlear and axillary, or the submaxillary and submental. There is no regional relationship to the lesions of the skin.

Kissmeyer (17), whose monograph is based on data from 250 reported cases and on personal observation of 28 patients encountered among 35 seen at the Finsen Institute, emphasizes the frequency with which the bronchial lymph nodes, the lungs and the bones are affected. X-rays of the chest disclosed enlarged peribronchial lymph nodes in 19 of 24 cases and in 15 of the 19 there were increased hilus shadows. In five cases the lungs showed the marbled or reticulated appearance referred to by many authors which produces an effect that may resemble miliary tuberculosis or the shadows observed in some instances of pneumonokoniosis. A characteristic of these shadows is that they extend from the roots of the lung towards the bases and not usually in the direction of the upper lobes or apices. In four of Goeckerman's (16) seventeen cases the lungs showed abnormal shadows in the X-ray.

Kirklin and Morton (24) have published excellent reproductions of the radiological appearance of the chest in four patients in whom the bronchial lymph nodes or lungs were affected. The most frequent

changes are seen at the roots of the lungs, and are usually bilateral. In this region there are large dense shadows with radiations extending into the lung fields, most often directed along the medial portion of the lower lobes towards the bases. In addition to these changes, there may be a fine reticulation of the lung. This usually is observed in the lower lobes. Occasionally shadows, such as those produced by enlarged lymph nodes, fill the superior mediastinum. These may occur with or without the changes in the lungs.

The clinical features attending the pulmonary disease in these patients are in many cases remarkable. Frequently there are no symptoms or physical signs that would indicate the presence of extensive disease of the lungs. As a rule there is little or no elevation of temperature; occasionally cough and expectoration occur. When the superior mediastinal and peribronchial lymph nodes are greatly enlarged, dulness over the manubrium and in the interscapular spaces is obtained, and there may be bronchovesicular modification of the breath sounds in these areas. Râles are rarely heard. The radiographic shadows may gradually recede and disappear entirely, or they may persist relatively unaltered for months or years (25). The condition is often referred to in the literature as a "tuberculide" or a benign form of disseminated tuberculosis. Bodecker (26) suggests that some of the cases reported as healed miliary tuberculosis of the lungs may belong to this group.

The alterations in the lung sometimes lead to a diffuse fibrosis. In association with these changes there may be cyanosis and progressive myocardial failure. Except for this complication the heart seems rarely to be affected, though Salvesen (33) noted in one of his patients transient bundle branch block that alternated with a regular rhythm.

The mucous membrane of the nose, the nasopharynx, the larynx and the conjunctivae may be involved. The tonsils are not infrequently affected (Pautrier (19)). The spleen and liver may enlarge.

The changes in the bones, so graphically described by Jüngling are very remarkable. The hands and feet are usually affected, but in rare instances the long bones of the extremities are involved. Occasionally there is no external evidence of disease, but usually the fingers are irregularly enlarged, the tips squared, with some dorsal flexion of the last phalanx. Fairly often the fingers are deformed by subcu-

taneous nodules that are symmetrically disposed about the interphalangeal joints. In advanced cases there may be relatively painless mutilation with gradual disappearance of the terminal phalanges. The appearance in the radiogram is characteristic. There are areas of rarefaction and reticulation distributed through the medulla of the phalanges, sometimes with irregular enlargement and distortion of the bones, but without involvement of the periosteum or of the joints. In many cases the areas of rarefaction occur as sharply defined round punched out spots. Jüngling held that these holes might represent an advanced and healing stage of the process.

Particular interest is attached to the changes that have been encountered in the eye. Iritis is frequently referred to as one manifestation of the disease. Blegvad (27) records cases with involvement of the conjunctivae, and Mylius (28) reports an instance of bilateral iridocyclitis.

The lachrymal and parotid glands are at times enlarged and show the lesions typical of sarcoid. Lesions are also said to occur in the mammary glands (Goeckerman), in the epididymis and in the testicle (Pautrier).

Though the nervous system appears usually to escape in this process, it is not entirely immune, for Reis and Rothfeld (29) have reported a case of sarcoid terminating with convulsive seizures in a girl of 17, who showed changes in the skin and bones. At autopsy, a tumor-like mass composed of tissue typical histologically of sarcoid was found upon the optic nerve. It seems probable that this same case has also been recorded by Lenartowicz and Rothfeld (30) who described an involvement of the skin, bronchial and mesenteric lymph nodes, spleen, liver and brain in a miliary sarcoid.

Homans (31) has referred to the tubercle-like lesions that may be found in the wall of the intestine and mesenteric lymph nodes in cases of regional ileitis, but in remarking upon their similarity to sarcoid he is not inclined to regard the lesions as of this nature, but as probably induced by reaction to a foreign body, which he thinks may be some form of fat.

In addition to the situations already noted, characteristic lesions have been described in the pleura, pericardium, the skeletal muscles and tendon sheaths, in the pituitary gland and in the prostate. It,

thus, seems probable that practically any organ or tissue in the body may be affected, and at autopsy miliary lupoid has been found disseminated throughout the body in much the same manner as miliary tuberculosis (14).

The changes occurring in the blood have been commented upon by Kissmeyer (17) and by Chevallier and Ely (32), who point out that there may at times be slight anaemia, though this is not usual. The total number of leucocytes is within normal limits, but a relative increase in the monocytes may occur. Salvesen (33) has observed a very striking increase in the total serum proteins in three out of four cases of generalized sarcoid which he has recently reported. The total serum proteins varied from 9.0 to 9.69 grams per cent. The unusual figure was due principally to an increase in the globulin fraction which he found elevated to from 5.05 to 6.10 grams per cent.

Many descriptions have been published of the pathological lesions in the skin, but in addition, changes of precisely the same character have been repeatedly observed in the lymph glands and in many of the internal organs. These lesions appear as collections of large, palely staining, epithelioid cells arranged in the form of miliary tubercles, sometimes lying as isolated structures in a comparatively normal tissue, and sometimes occurring in groups or strands. These collections of cells may attain such large proportions that they replace most of the normal tissue. They are not, as a rule, outlined by an inflammatory zone of lymphoid cells, and a characteristic feature is the absence of inflammatory reaction in the surrounding tissue. Occasionally large palely staining giant cells occur at the center or more rarely at the periphery of the "tubercle." In some instances there are a few necrotic cells in the center, but the absence of caseation has attracted the attention of almost everyone who has written on the subject. The lesion resembles and has frequently been referred to as an epithelioid (miliary) tubercle or as a "hard tubercle." It is noteworthy that the lesion retains this appearance in sections of the skin or lymph nodes that have been affected for months or even years. Healing may, however, occur through fibrosis. There are comparatively few accounts of the appearance of the lesions in the internal organs, but Beitema (34) has described and illustrated the miliary nodules in the lung, found accidentally by Dr. Deelman at

autopsy. Here, too, as in the skin and lymph nodes, the miliary lupoid lies isolated in the alveolar wall without a surrounding inflammatory reaction.

Reference has already been made to the pathological lesions found by Lenartowicz and Rothfeld (30) at autopsy. An elaborate pathological study of two fatal cases has been published by Mylius and Schürmann (35). In one patient the eye was affected and in addition to this the skin, bones and lymph nodes showed lesions resembling epithelioid tubercles, such as are universally described in Boeck's sarcoid. The lungs showed two distinct types of lesion that were readily distinguishable; one conforming to the epithelioid tubercle seen in the lymph nodes and skin, the other reproducing the usual picture of caseating tuberculosis. During life the skin reaction to both human and bovine tuberculin was negative, inoculations of tissue from the skin and finger, as well as of blood and sputum, did not produce tuberculosis in guinea-pigs and rabbits, and tubercle bacilli could not be demonstrated in the tissue removed at autopsy from the mass containing epithelioid tubercles. In the second case, a mediastinal mass, thought to be due to Hodgkin's disease, proved to be a huge agglomeration of lymph nodes, filled with miliary epithelioid tubercles, many of which were hyaline. Mylius and Schürmann suggest that the disease may be due to a modified form of the tubercle bacillus such as "B.C.G."

At the autopsy reported by Bernstein, Konzlemann and Sidlick (36) lesions were found on the eyelids and face, while nodules were discovered in the epicardium and in the intestines which were considered by them to show the histological changes encountered in instances of Boeck's sarcoid. Schaumann (14) has reported autopsies on four cases. One patient died of cardiac failure. There were extensive changes in the lungs and nodules on the epicardium. In addition the liver, spleen, lymph nodes, tonsils, bone marrow, pituitary and prostate were studded with nodules. The patient had given weakly positive or negative tuberculin reactions during life. Tubercle bacilli could not be demonstrated in the tonsils, and inoculations of material from many organs gave negative results in guinea-pigs. A second patient who had apparently recovered from sarcoid of the skin, lymph nodes and bones, later contracted tuberculosis from which she died.

At autopsy healed sarcoid was found in the bones and lymph nodes. A third patient supposed to have had diabetes insipidus died with tuberculosis of the peritoneum and lungs, but in addition showed the lesions typical of miliary sarcoid in many organs. In a fourth case characteristic lesions were found widely disseminated through the organs of a patient in whom the disease was not suspected and who had died of influenza. Schaumann emphasizes, in describing these cases, the fact that the disease is always more or less generalized, and that it has a predilection for lymphoid tissue.

The appearance of the pathological lesion has led almost inevitably to the belief that the disease is tuberculosis, but this contention has never been successfully proved, and has resulted in endless controversy on the subject. The disease rarely occurs in tuberculous families, and Lomholt (37) has shown that most of his 49 cases in Denmark came from rural districts where tuberculosis was least common. Though cases of sarcoid have been reported which later developed pulmonary tuberculosis (Boeck; Funk (38)), Kissmeyer (39) states that clinical tuberculosis occurs in scarcely 10 per cent of the cases. Schaumann (40) has reported a case in which with the evolution of pulmonary tuberculosis due to the bovine type of bacillus there was spontaneous disappearance of the sarcoids of the skin, lymph nodes and fingers.

In one of Jüngling's 10 cases there was tuberculosis of the vertebrae. Jacobsen (41) has recently reported a remarkable instance of cystic disease of many bones which he believes should be classed with the cases described by Jüngling. In Jacobson's case, the phalanges of hands and most of the metacarpal and many metatarsal bones, the right humerus, ulna and tibia, and the left humerus, ulna, radius and tibia were affected. This extensive disease of the bones was associated with widespread enlargement of lymph nodes, including the peribronchial nodes and was accompanied by a disseminated caseous tuberculosis from which tubercle bacilli of human type were cultivated. A sister died with generalized enlargement of the lymph nodes and splenic tumor. Sections of a cubital lymph node from this second patient showed a picture simulating sarcoid. The tuberculin test was negative (5 mg. intracutaneously) and portions of the lymph node inoculated into guinea-pigs did not produce tuberculosis. Martenstein (15) collected 98 cases of sarcoid and lupus pernio from the litera-

ture; 18 of these were definitely associated with tuberculosis, in 8 the association was questionable and in 72 there was no known tuberculosis.

The frequency with which the tuberculin reaction is negative in Boeck's sarcoid has aroused much interest. Jüngling quotes Helen Loewe as stating that the Von Pirquet reaction was negative in 73 per cent of 46 cases of "lupus pernio" and in 62 per cent of 82 cases of sarcoid. The intracutaneous reaction was negative in 60 per cent of cases of "lupus pernio" and in 33 per cent of cases of sarcoid. Schaumann (14) states that he has never seen a positive tuberculin reaction in uncomplicated "Benign lymphogranuloma." Kissmeyer (17) found that a positive tuberculin reaction was noted in about 40 per cent of the reported cases, and that when it occurred, it was usually mild. He concluded that the incidence of positive tuberculin reactions was approximately that which one would expect in any group of patients of the same age who did not have clinical tuberculosis. Kissmeyer also found that a focal tuberculin reaction was quite as unusual as a skin reaction. Of 18 reported attempts to produce this reaction, 15 were negative. Of 9 attempts to produce this reaction in his own patients all proved negative. Lomholt (42) in his 49 cases of sarcoid found the tuberculin reaction negative in 72 per cent; questionable in 8 per cent, mildly positive in 18 per cent and strongly positive in only 2 per cent.

There is consequently general unanimity of opinion that the tuberculin reaction is negative in a large majority of instances of sarcoid. Those who uphold strongly the view that the disease is caused by a reaction to tubercle bacilli (Boeck, Schaumann, Jüngling, Martenstein, Goeckerman and others) explain the lack of skin sensitiveness upon Jadassohn's theory of anergy. There are, however, cases on record in which a patient with sarcoid who gave a negative reaction showed later a positive tuberculin reaction after the development of proven pulmonary tuberculosis (Funk (38); Schaumann (14, 40)), or after treatment with tuberculin (Stein (43)).

It is generally recognized, too, that acid-fast bacilli can rarely if ever be found in the lesions of the skin or lymph nodes. Boeck reported one case in which scrapings from the mucous lesion in the nose showed acid-fast bacilli, and Dittrich (44) states that he has found

acid-fast bacilli in the lesions of the skin from two cases. It is usually noted in the literature that acid-fast bacilli are not found in the lesions.

The results of inoculations into animals has been as unsatisfactory as the other methods in attempting to demonstrate the tuberculous origin of the lesions of sarcoid. Kissmeyer states that in 39 collected cases in which inoculations were made all but 7 were negative. In 4 of these 7 he considered that the usual form of tuberculosis was also present. Jüngling, however, reports one positive result with inoculations of a subcutaneous node, the guinea-pig dying of tuberculosis in 7 months. Pautrier (45) reports one positive inoculation from the lymph node of a patient giving a positive tuberculin reaction.

On the other hand, some investigators and particularly Schaumann (40) and Romel (46) have stated that though tuberculosis was not produced by inoculating material from cases of sarcoid in the first generation of guinea-pigs, the further inoculations of lymph nodes from the first generation of guinea-pigs through two or three generations resulted in some instances in the production of tuberculosis. It has been suggested that in such instances the disease was caused by a "filterable" form of the tubercle bacillus.

As one reviews the published data, it must be concluded that there is little direct proof that the lesions of "sarcoid" are caused by the tubercle bacillus, or indeed, as has been suggested by several investigators, by the action of the products of its growth. The view prevails at the present time, however, that the disease is a peculiar form of benign tuberculosis.

A few investigators have always opposed this conception. Kuznitzky and Bittorf (12) believed that it was not tuberculosis but was a granuloma produced by some other specific infection. Kissmeyer (17, 39); Lomholt (37, 42); and Nielsen (47) are of the same opinion. Kissmeyer and Nielsen (48) have discussed at some length the etiology of the disease. They believe that it is not tuberculosis and point out that the bone lesions resemble more nearly those of leprosy than those of either tuberculosis or syphilis. They suggest that the disease is caused by some specific agent, perhaps nearly allied to the lepra bacillus, but producing a peculiar form of chronic granuloma different from either tuberculosis or leprosy.

It has been pointed out by a number of observers that known forms

of infection other than tuberculosis may cause lesions in various situations that are much like those so familiar in sarcoid. Reference has already been made to the resemblance of the bone lesions to those of leprosy. Murdock and Hutter (49) state that the sarcoid of Boeck is the only disease in which the changes in the small bones of the hand simulate closely those found in leprosy. Motta (50) refers to a case of leprosy developing skin lesions thought to have the histological appearance of Boeck's Sarcoid, and Pautrier (51), who is very familiar with the pathology of sarcoid, describes a case of tuberculoid leprosy of the forearm presenting the typical histological picture of Boeck's sarcoid. Leprosy bacilli were not found in the sections, and the tissue inoculated into guinea-pigs and Macacus monkeys gave negative results.

It has also been stated (Dupont (51)) that Leishmania may produce a cutaneous lesion which has some likeness to Boeck's sarcoid. Though Leishmania may be found in the tissues in the early stages, they disappear from the older lesions.

Williams and Nickerson (52) have reported interesting observations on a skin reaction to an emulsion of a skin lesion in patients suffering with sarcoid. The intracutaneous injection of from 0.05 to 0.15 cc. of this emulsion in four patients with lesions considered to be those of sarcoid of Boeck resulted in the appearance of a red papule within 36 hours. Two of the patients had been subjected to splenectomy, two had been operated on for disease of the ileum, in one case diagnosed "regional ileitis." Four normal individuals showed no skin reaction to intracutaneous injection of the emulsion. They suggest, from their results, that the disease may be caused by a filterable virus.

The entire subject is perhaps further confused by the fact that subcutaneous injections of paraffin, oils and fats may give rise to a foreign-body reaction which often resembles a tubercle or sarcoid (Gougerat (53); Joltrain (54)). In this connection it is important to recall the work of Sabin, Doan and Forkner (55) on the reactions of the connective tissues of normal animals to the lipoids of the tubercle bacillus. A phosphatide fraction A-3 was particularly potent in calling forth the production of epithelioid cells and giant cells which were frequently arranged in tubercle formation. When the injections of phosphatide were stopped, the tuberculoid tissue underwent resolution and grad-

ually disappeared. Some of the illustrations showing the effects of the phosphatide A-3 are not unlike the lesions encountered in Boeck's sarcoid.

Though the disseminated sarcoid of Boeck pursues a chronic and often benign course, spontaneous healing of the lesions may occur. The changes in the lung may disappear entirely and even the lesions in the bones may subside. In many cases, however, the disease lasts for years. It may relapse, involving one organ after another. In the meantime healing of some of the lesions may take place.

The disease has been found highly refractory to treatment. Arsenic in various forms has been employed by most observers. Finsen ray, ultra-violet light, X-ray and radium have also been employed. Lomholt (56) has recently reported beneficial effects, particularly upon the lesions of the mucous membranes, in 12 cases following the intramuscular injections of "Antileprol," a preparation which is extracted in part from chaulmoogra oil.

Though a chronic benign affection of the lymph nodes, which showed histological lesions surprisingly like those of miliary tuberculosis has been familiar to me for many years, it is only recently that this form of glandular enlargement has been identified with the well characterized clinical picture of Boeck's sarcoid. The earlier cases, of which there were four, were observed at the Pennsylvania Hospital, Philadelphia, between 1902 and 1905. Recently Dr. Bauer of the Pennsylvania Hospital has very kindly examined a larger number of sections from lymph nodes removed at operation at the Pennsylvania Hospital and has found five more cases in which the pathological picture in the lymph nodes is that of Boeck's sarcoid. I am indebted both to Dr. Bauer and to the surgeons in charge for permission to mention these cases.

Since 1923 eight patients in whom the disease presented the clinical and pathological features of generalized sarcoid have been studied at the Johns Hopkins Hospital, and the specimen of a lymph node has been obtained from one patient who was seen at the Baltimore City Hospital through the kindness of Dr. Thomas R. Boggs.

Only eight of these cases have been studied in sufficient detail to be accurately recorded.

Case 1. E. W. aged 38, female, colored, housewife. Unit no. 50444. Admitted to Johns Hopkins Hospital December 14, 1923, complaining of "Knots in the neck." Mother had died of dropsy at 30, and father of Bright's disease at 66. Two sisters had had swollen glands in the neck. There was no "consumption" in the family. The patient had been a delicate child; had had measles, mumps, pertussis and chickenpox in childhood, and pneumonia at 24 and at 29. Had had frequent colds but otherwise excellent health for last ten years. Married, two miscarriages, no children.

In April 1922, 20 months before admission, swellings appeared under the chin; she noticed that her heart "jerked," and that she was slightly short of breath on exertion and at night. Six months later other swellings appeared under her jaws and increased rapidly in size. They were not tender. Two months ago swellings appeared in back of neck, above clavicles, and in cubital region. Two weeks ago swellings appeared in the axillae. During the twenty months she has felt quite well, has had no fever, and dyspnoea has improved. She has lost 11 pounds in weight in the last two years.

On admission, Temp. 99°; pulse 88; resp. 16; B.P. 120/84. She was a well developed colored woman without eruptions on the skin or abnormalities of the bones. Examination of nose and throat showed nothing abnormal. There was a marked general enlargement of lymph nodes. In the anterior cervical triangle they caused the neck to bulge and there were swellings in the pre-auricular and submental regions (Fig. 1). Axillary, epitrochlear and inguinal nodes were also much enlarged. The nodes were freely movable, discrete and not tender. Pupils equal, conjunctivae normal. Left retina showed a group of small white punctate exudates. There was dulness beneath the manubrium and in the interscapular spaces posteriorly. Breath sounds in the interscapular spaces were bronchovesicular and whisper on the right was tubular in quality. There were no râles even after coughing. The area of cardiac dulness was not enlarged. P.M.I. was felt in the 5th space in midclavicular line; dulness reached 8 cm. to left in 4th space. Sounds loud with a high-pitched systolic murmur at the apex. The liver edge was felt 3 cm. below the costal margin in the right midclavicular line; spleen not palpable. Examination of extremities and nervous system showed no abnormalities. Hb. 80%, red blood cells 4,300,000, leucocytes 4,150, polymorphonuclears 71%, eosinophiles 2%, basophiles 1%, lymphocytes 19%, monocytes 7%. Urine: acid, sp. gr. 1017, no albumin, no sugar; microscopical examination showed no abnormalities. Wassermann reaction negative. Dec. 19—excision of inguinal lymph node. Dec. 20, 1923—reaction negative to 1 mg. of tuberculin (O.T.) intracutaneously. Dec. 21—x-ray of chest showed mass in upper mediastinum suggesting glandular enlargement with root infiltration on both sides (Fig. 2). The temperature ranged from 97° to 100°; the pulse from 96 to 100. The patient was treated with radium without immediate benefit.

Sections of the lymph node showed that it had been almost entirely replaced by miliary collections of large pale epithelioid cells, some of which were partly hyaline; in the center of others a giant cell was occasionally seen. There was no

infiltration of cells about the epithelioid nests, but many were separated by connective tissue or hyaline bands (Fig. 3).

Summary: Progressive enlargement of lymph nodes for 20 months in a colored woman of 38; dyspnoea and occasional cough without fever or other marked constitutional symptoms. Mass in mediastinum with infiltration of roots of lungs; enlargement of liver. No changes observed in skin or bones. Negative tuberculin reaction. Lymph nodes showed miliary collections of epithelioid cells. Clinical diagnosis Hodgkin's disease; microscopical diagnosis tuberculosis; revised diagnosis "Sarcoid."

The essential feature of this case was the progressive and pronounced general enlargement of the superficial lymph nodes, with clinical and roentgenological evidences of a large mass in the superior mediastinum and infiltration at the roots of the lung. Dyspnoea was the only constitutional symptom. The skin was not affected and the bones were normal to clinical examination. The intracutaneous tuberculin reaction was negative to 1.0 mg. of tuberculin. A section of the inguinal lymph node showed the characteristic histological changes of Boeck's sarcoid. The further course of the disease is unknown, since the patient did not return to the hospital, and cannot be located.

Case 2. T. M. Male, colored, aged 14. Unit no. 2787. Admitted to the Johns Hopkins Hospital Feb. 16, 1926, complaining of "lumps in neck and back of head" of one year's duration. Father and mother alive and well. One brother had died in his fourth year from influenza. There was no history of tuberculosis in the family.

Generally, he had been healthy. He had had pneumonia when an infant; measles and whooping cough at 12.

In April 1925, 10 months before admission, symmetrical swellings appeared behind and in front of the ears which were thought to be mumps. There was no pain but possibly some fever. The masses increased slightly in size, then remained stationary until 3 weeks before admission when swellings appeared in posterior and in anterior regions of neck. There had been no fever, night sweats, pain, dyspnoea nor loss of weight.

On admission, Temp. 99.6°; pulse 84; respirations 20. He was a well nourished mulatto boy who did not appear sick. The skin, bones and joints appeared normal. Three accessory nipples were seen on the right side. Upper eyelids were puffy and lachrymal glands looked somewhat enlarged. Fundi normal; tonsils somewhat enlarged; the thyroid was normal. There was well marked generalized enlargement of lymph nodes, affecting those of both triangles of neck, pre-auricular and postauricular, submaxillaries, axillaries, inguinals and femorals

(Fig. 4). The epitrochlears were not felt. Glands varied from size of a pea to 2 cm. in diameter; smooth, rubbery, not tender, freely movable. The lungs were clear to percussion and auscultation. The heart was not enlarged; P.M.I. in 5th space 7 cm. from midline. The sounds were normal; rhythm regular. B.P. 100/60. The abdomen was soft; spleen and liver were not palpable. The neurological examination showed nothing abnormal. Hb. 90%; red blood cells 5,300,000; leucocytes 5,950; polymorphonuclears 58%, eosinophiles 3.5%; lymphocytes 33%; monocytes 5%; basophiles 0.5%. Wassermann negative. Urine: acid, amber, sp. gr. 1020, no sugar, no albumin. Sediment showed no abnormalities. A lymph node was excised from the cervical region and right axilla. The patient was discharged in March 1926.

He appeared in the medical dispensary on July 9, 1930 with an eruption over the face, ears and neck of six months' duration. It consisted of raised, solitary and grouped pinkish or yellowish nodules which were seen also on the eyelids and forearms. The submaxillary and pre-auricular lymph nodes were enlarged (Fig. 5). A photograph made at this time showed definite bulbous swelling of the phalanges with squaring of tips of fingers (Fig. 6). The Wassermann reaction was positive and the patient was treated from July 19, 1930 to Dec. 19, 1930 with arsphenamine, bismuth and finally silver arsphenamine without obvious effect upon the eruption but with reversion of the Wassermann to negative. In Dec. 1930 an X-ray of the chest showed increased root shadows with extension into the right lung suggesting an active process (Fig. 7). Sections of the skin made July 9, 1930 did not include an entire nodule, but showed in one place collections of epithelioid cells similar to those of the miliary nodule of sarcoid.

After Dec. 1930 he was not seen again until Jan. 15, 1936, ten years after his first admission. Except for the eruption which had cleared and had left very large elevated scars (keloids) he had been well. He appeared healthy, muscular and perfectly well. There were large keloids covering part of the nape of neck and one or two on left shoulder. The superficial lymph nodes were scarcely palpable but quite firm. The heart and lungs were normal. An X-ray of the chest showed no abnormalities (Fig. 8). The liver and spleen were not palpable. The hands appeared quite abnormal (Fig. 9). The fingers were somewhat distorted with dorsal depressions on most of the middle phalanges. They looked shortened and the tips of the first and third finger and thumb on left were capped with short square nails. There was a moderate dorsal flexion of the last phalanges. There were no swellings about the interphalangeal joints. The patient was unaware of any change in his hands. There had been no pain, no difficulty in manipulation. X-rays showed irregular areas of rarefaction in phalanges of thumbs and all fingers, and in the 5th metacarpal bones (Fig. 10). In most of the phalanges there were small punched-out areas. The periosteum and joints remained intact.

There were no other abnormalities found on physical examination. Blood non-protein nitrogen 34 mgs. %; total blood proteins 7.32 mgs. %; albumin 4.31 gms. % and globulin 3.0 gms. %. Hb. 89%; Leucocytes 4,750, polymorphonuclears 69%, eosinophiles 3%, lymphocytes 18%, monocytes 10%.

The lymph nodes removed from the cervical and axillary region in 1926 showed on section almost complete replacement of the lymphoid tissue by miliary arrangements of epithelioid cells, usually occurring in clumps, but sometimes separated by comparatively normal lymphoid tissue. A few giant cells were seen and in some of the larger collections of epithelioid tubercles there was a central area of vacuolated necrosis (Fig. 11).

Mar. 4, 1926, a portion of a lymph node was inoculated into 4 guinea-pigs by Dr. Willis. Cultures were made from the emulsions of lymph nodes on Petroff's medium and on blood agar, but no growth was obtained. One guinea-pig died 4 weeks after inoculation but showed no tuberculosis. One guinea-pig was sacrificed 3 months after inoculation; all the tissues appeared normal and sections from inguinal, iliac and tracheo-bronchial lymph nodes failed to show tuberculous tissue or tubercle bacilli. Two guinea-pigs remained well for more than a year.

Summary: Progressive enlargement of superficial lymph nodes for a year in a negro, aged 14, with possible involvement of the parotid and lachrymal glands, without constitutional symptoms. Clinical diagnosis, Hodgkin's disease. Microscopical diagnosis of lymph nodes, miliary tuberculosis. Gradual subsidence of lymph nodes. Appearance of skin eruption, lesions in bones of hands and shadows in X-ray of lungs 4 years later. Clinical diagnosis at this time, tuberculosis or syphilis. Asymptomatic for next 6 years when moderately advanced changes in the bones of hands were discovered on examination and in the radiogram. The eruption on skin and shadows in the lungs had completely disappeared. Revised diagnosis Boeck's sarcoid.

In this patient the first evidence of the disease appeared as a general enlargement of the superficial lymph nodes with negligible constitutional disturbances. It is worthy of note that the parotid glands were probably involved and the lachrymal glands definitely enlarged. The gradual recovery from the general glandular enlargement was followed 4 years later by a relapse with appearance of skin lesions, pulmonary involvement, and alterations in bones of hands. Six years later, and 10 years after the first symptoms appeared, he was physically well and there only remained keloids on the neck and what appeared to be healing lesions in the phalanges of the hands. The case is an example of the benign protracted and relapsing nature of the disease. At the time when the bones of the hand were affected, the proteins of the blood were not elevated above the limits of normal. The inoculations of lymph nodes into guinea-pigs, and cultures from the nodes on Petroff's medium and blood agar all gave negative results.

Case 3. R. G. Female, colored, aged 24. Unit no. 9440. Admitted to the Johns Hopkins Hospital Dec. 15, 1926, complaining of swelling in the neck and

groin for one year. Father living and well; mother died suddenly of unknown cause; 3 sisters living and well; no known tuberculosis in the family. Has always been healthy; mumps and whooping cough as a child and pneumonia at 24. She "catches cold" easily. Menstruation regular; has been married four years; two children living and well, no miscarriages.

One year before admission noticed small lump below angle of left jaw which grew smaller and then increased in size 4 months ago. Shortly afterwards swellings apppeared on left side of face, at angle of right jaw and later in inguinal regions. For one week there has been pain at angle of jaw when eating. There has been no pain elsewhere, no tenderness of swellings, no fever, no loss of strength, no dyspnoea, no itching of skin, but possibly some loss of weight. The patient has continued to work without discomfort.

On physical examination, temperature 98.6, pulse 100, respirations 18. She was well developed, slightly undernourished, without dyspnoea. There were no eruptions on skin, no abnormalities of bones or joints. The eyes and fundi appeared normal, thyroid gland slightly enlarged; veins of the neck full. Marked general enlargement of the lymph nodes particularly in the pre-auricular and postauricular regions and about the angles of jaws, where they tended to form a collar (Fig. 12). There were smaller nodes in the cervical and supraclavicular regions, large ones in the axillary, inguinal, femoral and iliac regions. The epitrochlears were palpable and there were small nodes about the right breast. The nodes varied from 0.5 to 3 cm. in diameter, were firm, oval, freely movable, not tender. The chest was flattened, there was dulness beneath the manubrium and about the spines of the scapulae. Over manubrium and in interscapular spaces, breath sounds were bronchovesicular, without râles; elsewhere lungs were clear to percussion and auscultation. Heart not enlarged, dulness in 5th interspace 9.5 cm. to left. Heart sounds clear, with accentuation of second aortic sound; rhythm regular, B.P. 135/85.

Abdomen rather tense, slightly tender in right upper quadrant. Liver and spleen not palpable. Rectal and neurological examinations showed nothing abnormal. Wassermann negative. Hb. 70%; red blood cells 4,520,000; leucocytes 8,200; polymorphonuclears 53%, eosinophiles 22%, lymphocytes 15%, monocytes 11%. Urine clear, sp. gr. 1022, acid, no sugar, albumin trace, sediment showed a few leucocytes.

12/16/26: X-ray of chest showed a large mediastinal shadow with infiltration extending from roots of lung and fine reticular shadows through lower lobes (Fig. 13).

12/20/26: Cervical lymph node removed for diagnosis.

12/27: Leucocytes 4,400; polymorphonuclears 70%; eosinophiles 12%; lymphocytes 12%; monocytes 6%. 1/5/27: Treatment started with ultraviolet light.

1/12: Intracutaneous tuberculin test 0.1 mg. of O.T. and avian negative.

1/15: Intracutaneous tuberculin test 1.0 mg. of O.T. and avian—slight reaction to both after 5 days. The patient gradually improved, the eosinophilia persisted.

1/11/37: Leucocytes 4,600; polymorphonuclears 29%; eosinophiles 35%; lympho-

cytes 20%; monocytes 15%. By Jan. 26, 1927, the lymph nodes had diminished definitely in size. She was discharged Jan. 30, 1927.

During her stay in the hospital the rectal temperature varied usually between 98.2° and 99.8°, on a few occasions reaching 100° and rarely 100.4°F. During the subsequent months the lymph nodes slowly decreased in size.

On Jan. 11, 1936, about 10 years after the onset of her disease, she stated that she had been well for many years. Examination of the skin, bony structures, heart, lungs and abdomen showed nothing abnormal. The superficial lymph nodes were not palpable. A radiogram of the chest showed the lungs and mediastinum to be clear (Fig. 14).

Sections of the cervical lymph node, removed 12/20/26, showed replacement of the lymphoid tissue by solitary epithelioid nests and by clumps of these tubercle-like structures often separated by connective tissue or hyaline material. Central giant cells numerous, and some of the miliary epithelioid collections of cells showed small areas of central necrosis. Cultures from the node were made by Dr. Willis on Dorset's and Petroff's media. Emulsions were inoculated subcutaneously into 2 guinea-pigs and 2 rabbits, and intraperitoneally into 2 pigeons. One guinea-pig, 1 rabbit and 1 pigeon were sacrificed 2 months after inoculation. Guinea-pig and pigeon were normal. Rabbit showed a small abscess at point of inoculation. Remaining animals continued well.

Summary: Asymptomatic progressive enlargement of all the superficial lymph nodes in a colored woman of 24 with a large mass in superior mediastinum and infiltration of both lungs; eosinophilia. *Clinical diagnosis:* Hodgkin's disease. Microscopical diagnosis from lymph nodules, miliary tuberculosis. Gradual improvement with complete recovery. Revised diagnosis—generalized Boeck's sarcoid.

It is of particular interest in this case that, in addition to the widespread asymptomatic disease of the lymphatic system, affecting not only the superficial lymph nodes, but the superior mediastinal, peribronchial and iliac nodes, there should be a diffuse infiltration of the lower lobes of the lungs and a pronounced and unexplained eosinophilia. An improvement in the patient's condition began while she was still under observation and continued until complete recovery ensued. There were never at any time lesions in the skin and no abnormalities of the bones were ever observed. It is problematical whether treatment with ultraviolet light had any effect upon the course of the disease, though improvement started during the course of this treatment. The case illustrates in a striking manner how widespread the disease may become without involvement of the skin and how all evidence of extensive disease of the mediastinum and lungs

may entirely disappear. In this patient the intracutaneous reaction to the human and avian tuberculin was negative to 0.1 mg., and doubtful to 1.0 mg.; and cultures from the glands on Dorset's egg medium and Petroff's medium, as well as inoculations of the gland emulsions into guinea-pigs, rabbits and pigeons, gave negative results.

Case 4 V. G. (Unit no. 23,175). An unmarried colored girl, aged 21 years, was admitted to the Johns Hopkins Hospital Feb. 13, 1929. The patient was carefully studied by Dr. James Bordley III. She complained of "breaking out" on her face and a "sore" on her leg. Father and mother were living and well; twelve brothers and sisters alive and well. There was no history in the family suggestive of tuberculosis. Lived on farm and except for measles and mumps had never been ill.

In the autumn of 1922, about 7 years before admission, a cow had stepped on her left foot, tearing the skin between the first and second toes. This did not heal for 2–3 weeks. In the summer of 1923, about 6 months later, a small moderately painful lump appeared on left shin, gradually increasing in size and finally rupturing, leaving a raw area which had never healed. Two years later, in 1925, "inflammation" developed about nail of fourth left finger, after which the finger became "puffed up" and moderately painful. Swelling subsided, leaving finger and nail distorted. Later similar swellings appeared at different times on almost all fingers. Four years ago (1925) whitish areas appeared on arms; three years ago (1926) nose became swollen and eruption spread from nose over cheeks. Six months before admission hoarseness appeared. She had not felt sick and had gained weight normally. She had not had fever, sweats, chills or cough. She had had three injections of "salvarsan" in 1928.

On examination temp. 99.2°, pulse 88, respirations 20. She appeared well nourished, was very hoarse, showed respiratory stridor but no dyspnoea. Area of reduced pigmentation was visible over bridge of nose and cheeks with a few soft pinkish nodules 2 to 3 cm. in diameter scattered through it; larger wart-like nodules were prominent on left cheek and upper lip. The left ala nasi looked large and felt thick and nodular. The nose was broad and the nasal mucosa swollen and oedematous (Fig. 15). Over upper arms and forearms there were rubbery nodules surrounded by areas of reduced pigmentation. A shallow ulcer, 2 cm. x 5 cm., with granulating base was seen on left tibia. Small firm lymph nodes were felt in all cervical triangles; axillaries were larger, reaching 1.0 cm. in diameter, epitrochlears equally large, inguinals slightly enlarged. All nodes were freely movable, not tender. The lower ends of the radii and ulnae were definitely enlarged and the hands showed the most extraordinary deformities best illustrated in Fig. 16. They were short, thick, showed ulnar deflection with soft almost fluctuant swellings about many of finger joints. The nails were short, thick and showed longitudinal striations, and some were split. In spite of these deformities the joints appeared normal, the function unimpaired and the patient could use her hands freely. The projections about 1 cm. in diameter, seen on left of tibia near its

upper extremity, and the lower ends of tibiae were slightly enlarged and irregular. Radiograms of hands and feet showed web-like rarefaction with cystoid lesions in the metacarpals, metatarsals and phalanges (Figs. 17 and 18); lace-like rarefaction involved the lower ends of radii and ulnae, the lower ends of humeri, upper ends of ulnae and lower ends of tibiae and fibulae. The joints were not affected and the periosteum not diseased except in the tibia beneath the ulcer. Tiny reddish papules were seen on hard palate. General oedema of epiglottis and laryngeal structures. Lungs clear to auscultation and percussion. The heart was not enlarged, the cardiac sounds were clear. The liver was not palpable, but the spleen could be felt 4 cm. below the costal margin. There was profuse leucorrheal discharge. The neurological examination showed nothing abnormal. Hb. 61%, red blood cells 3,780,000, leucocytes 4,960, polymorphonuclears 59.8%, eosinophiles 4%, lymphocytes 27.9%, monocytes 9.1%. Urine normal except for leucocytes in sediment. No Bence-Jones protein. Wassermann reaction negative. Von Pirquet negative. Intracutaneous tuberculin tests with 0.1 and 0.5 mg. of O.T. negative. Blood serum calcium 10.8 mg. %. Blood serum inorganic phosphate, 4.4 mg. X-ray films of chest showed enlarged mediastinal glands and increased shadows at the roots of lung, most marked on right and extending to the base near mediastinum (Fig. 19). For two weeks the rectal temperature reached 100°–100.6° almost every evening, but subsequently the temperature remained normal. She gained weight, the anaemia diminished and the leg ulcer improved. On the 4th 11th and 19th of March she received 0.3 gram of neoarsphenamine intravenously. She was treated by ultraviolet light and given tuberculin therapy until October 1929 when she left Baltimore. Her condition was not materially changed at that time.

No spiral organisms, acid-fast bacilli or spores were ever found in the secretions from nose or leg ulcer. Cultures on ordinary laboratory media and Sabouraud's medium from these situations gave no positive results. Guinea-pigs injected with these materials showed no tuberculosis when sacrificed at the end of 6 weeks.

Sections of epitrochlear lymph nodes excised on Feb. 19th and Mar. 12th showed the gland almost replaced by miliary collections of epithelioid cells with a narrow rim of lymphoid tissue beneath the capsule of the gland. There were many central giant cells but no areas of necrosis (Fig. 20). Careful study of many reactions of these glands failed to show any acid-fast bacilli.

Material obtained from puncture of an epitrochlear lymph node on Feb. 17th was planted on Sabouraud's medium, and inoculated into the groin of a guinea-pig. No growth resulted and the guinea-pig sacrificed after six weeks did not show tuberculosis. A skin nodule and epitrochlear gland excised Feb. 19th was each ground, inoculated on Sabouraud's medium and into guinea-pigs. No growth resulted and the guinea-pigs sacrificed at the end of 6 weeks did not show tuberculosis. On Mar. 12th an epitrochlear gland was excised, emulsified and inoculated intraperitoneally into a guinea-pig and into two pigeons. The guinea-pig died one week after injection, but the pigeons, still healthy after ten weeks, were sacrificed. Their organs at autopsy were normal.

Summary: Injury to foot and ulcer of skin in girl of 14 followed two years

afterwards by appearance of nodules first on fingers, then on skin of face with subsequent enlargement of nose and finally development of hoarseness. The disease was widespread, affecting the skin of face, nose, nasal and laryngeal mucosa, lymph nodes, spleen, and many bones of the extremities. Intracutaneous tuberculin reaction negative; sections of lymph nodes showed lesions typical of sarcoid. Cultures and inoculation of material obtained from leg ulcer, nasal discharge, skin nodule and lymph nodes gave negative results.

This case is an example of the generalization of the disease, progressing practically without constitutional symptoms, and finally involving many structures and organs in the body without incapacitating the patient to any material extent. It is of particular interest that in addition to the extensive changes in the phalanges the disease affected the metacarpal and metatarsal bones, and the long bones of the arms and legs. The distribution is unusual though by no means unknown. Jüngling (10) found lesions in the long bones in one of his nine cases and Nielsen (41) refers to rare cases in which radiographic changes were found in the long bones, the nasal bones and in one case in the frontal bones. It is also noteworthy that the disease started at a very early age, and progressed during adolescence without retarding either the physical or mental development of the patient. It is quite characteristic that the body changes in this patient were associated with the form of cutaneous lesion usually designated as "Lupus pernio."

Sections of the lymph nodes showed the epithelioid tubercles characteristic of Boeck's sarcoid. Cultures from the mucous membranes, skin nodules, and lymph nodes on Sabouraud's medium showed no growth, and inoculations of these materials into guinea-pigs, and of a lymph node into pigeons gave negative results.

Case 5. S. H. (Unit no. 56800), an unmarried negro boy, aged 18, a farm laborer, was admitted to the Johns Hopkins Hospital on July 20, 1934, complaining of "cough and cold" and "little knots all over him." Mother and father were alive and well. One uncle had died of "tuberculosis."

He had always been very well except for frequent colds and childhood diseases. He had an attack of haematuria when 4½ months old and an attack of diarrhea at 13 with blood and mucus in stools. Usual weight 167 pounds.

Caught cold 4½ months before admission and coughed as if he had whooping cough. He had considerable yellowish sputum, pain in the chest and vomited after coughing. Occasionally nose bleeds occurred after coughing. He lost weight rapidly, at first 10 pounds a week. 3½ months ago became short of breath

and had palpitation and precordial pain on slightest exertion. At this time nodules size of pea appeared in skin over arms, flanks and upper legs. Some were slightly tender; some have disappeared. One month ago experienced constant aching pain in epigastrium and his hands and eyes became yellow. The pain disappeared shortly, the yellow color faded after 10 days. He had become nervous and four days ago had another attack of pain in epigastrium with vomiting. His present weight is 116 pounds so that he has lost approximately 50 pounds in weight during his illness. He appeared moderately emaciated, weak, with good color. No abnormalities of bones observed. Numerous nodules, size of small pea, felt in deep tissues, probably muscles of arms. They were not tender. No abnormalities of eyes noted. There was general enlargement of superficial lymph nodes. Supraclaviculars were as large as peach stones; right epitrochlear, size of almond. All nodes were soft, freely movable, discrete, not tender. Thyroid not enlarged. Retromanubrial dulness was not increased, and lungs were clear to percussion. A few râles heard at right apex posteriorly. Heart not enlarged; P.M.I. 5th space, 7 cm. to left; dulness 8.5 cm. to left. No murmurs heard, but second sound split at base. Liver and spleen were not felt. Right epididymis was enlarged and firm. Hb. 98%; R.B.C. 4,670,000; Leucocytes 4,500; polymorphonuclears 63%; eosinophiles 4%; lymphocytes 16%, monocytes 17%. Wassermann negative. Urine: sp. gr. 1014, acid, no albumin, no sugar, sediment showed a few leucocytes. X-ray of chest showed marked enlargement of mediastinal lymph nodes, infiltration of lungs, especially of right, suggesting either tuberculosis or Hodgkin's disease (Fig. 21). Bones of forearms normal. Sputum showed no tubercle bacilli in three examinations. 7/22: Leucocytes 3,850; polymorphonuclears 59%; eosinophiles 7%; lymphocytes 16%, monocytes 18%. Electrocardiogram showed normal sinus rhythm. 7/24: Excision of epitrochlear lymph node and subcutaneous nodule. 7/27: Intracutaneous tuberculin reaction with 0.01 mg. and 0.1 mg. (O.T.) negative. Slight dulness obtained in supraspinous regions. No râles heard on deep breathing. 8/4: Intracutaneous tuberculin 1.0 mg. (O.T.) negative. Rectal temperature varied from 98.6° to 100°, and on one or two occasions reached 101°.

Patient was discharged to a sanatorium in Virginia. On Feb. 13, 1935, Dr. Woodson reported that the patient had no skin lesions, "The condition of the lungs has not improved."

Sections of lymph node show the structure well preserved but studded with miliary nests of epithelioid cells, without a surrounding inflammatory zone. Some of the nests which resemble epithelioid miliary tubercles are surrounded by hyaline material. A few show large pale central giant cells. Occasionally there is a small central area of necrosis. There are no pyknotic nuclei either within or about these small areas of necrosis. Sections of the subcutaneous nodules showed that they involved, in part, the muscle which contained isolated and conglomerate nests of epithelioid cells precisely like those in the lymph nodes. There were no areas of necrosis. Cultures of subcutaneous nodules gave no growth. Acid-fast bacilli could not be found in sections.

Summary: Rapidly progressive illness over 4½ months with cough and loss of weight but very slight fever in a colored boy of 18. Enlargement of superficial and mediastinal lymph nodes with extensive involvement of the roots of lungs. Small nodules beneath the skin and in the muscles of arms and legs. Intracutaneous tuberculin reaction negative. No tubercle bacilli found in sputum. Disappearance of subcutaneous nodules. Pulmonary lesions practically unchanged after one and one-half years.

The process in this patient was noticeable on account of the pronounced symptoms which accompanied the progressive disease of the lungs and on account of the involvement of the muscles. It was thought at first that the patient might be suffering from Hodgkin's disease or an actively progressing tuberculosis. Though tubercle bacilli could never be found in the sputum and the tuberculin reaction was negative, it would be difficult to exclude pulmonary tuberculosis, in its usual form, as playing a part in the general clinical picture. It is probable, however, that the entire process can be attributed to an extensive involvement of the superficial lymph nodes, the mediastinum, lungs and muscles by Boeck's sarcoid.

Case 6. R. K. A single colored man, aged 28, a cooper by trade, (Unit no. 65712) was admitted to the Johns Hopkins Hospital on Oct. 25, 1935, complaining of jaundice. His father was living, his mother was dead and one sister had died of tuberculosis. He had had mumps, chickenpox and whooping cough in childhood, occasional sore throats but had been generally healthy. He had had gonorrhoea in 1930 and a chancre in Oct. 1934. His best weight was 156, his present weight 140.

In Oct. 1934, about one week prior to the appearance of chancre, he experienced discomfort in epigastrium, nausea, eructations and in a few days jaundice. Some weeks later a rash appeared over his back, he felt ill and jaundice deepened with clay-colored stools. He was admitted to City Hospitals and given two injections in arm over a period of ten days with immediate improvement. During winter of 1934 and 1935 he received injections into buttocks. In May 1935 had a second attack of nausea, jaundice and clay-colored stools. At this time it was found in Johns Hopkins Hospital Dispensary that he had jaundice, marked general glandular enlargement and pigmented macules over back. Liver and spleen were not palpable. X-ray of chest showed "fibroid induration" in upper portions of both lungs. He was given 3 intravenous injections of 0.2 gram of arsphenamine. After second injection jaundice disappeared. Wassermann negative at this time. After July 15, 1935 he received 8 injections into the arm at City Clinic. A week and a half before his admission, while he was still receiving injections, abdominal pain, nausea and jaundice returned.

On admission temperature was 98.6°, pulse 60, respirations 20. He was well developed; sclerae jaundiced; a few papules were seen on arms. There was very marked enlargement of cervical, pre- and post-auricular, inguinal and femoral lymph nodes, the femoral on the right being readily visible. The nodes were rubbery, freely movable, discrete and not tender. Heart not enlarged, sounds clear, lungs clear to percussion, a few râles heard over right lower lobe. Liver palpable 12 cm. below costal margin; spleen not felt. Neurological examination showed no abnormalities. Hb. 100%; red blood cells 4,900,000; leucocytes 11,300; polymorphonuclears 66%, eosinophiles 6%, basophiles 1%, lymphocytes 24%, monocytes 3%. Urine: sp., gr. 1023, acid, no sugar, no albumin, bile present, microscopically, a few leucocytes. Wassermann negative; nonprotein nitrogen of blood 26 mgm. %. X-ray of gastrointestinal tract showed no abnormalities. 10/29: X-ray of chest shows old fibroid infiltration of both lungs, more accentuated in right upper with large calcium deposit. Part of shadow suggests occupational disease (Fig. 22). Intracutaneous tuberculin with O.T. negative up to 0.1 mg. 11/14: Agglutination with Brucella abortus, melitensis and suis negative. 11/19: Excision of cervical lymph node for examination.

Under treatment with ultraviolet light and intravenous injections of neoarsphenamine the patient improved somewhat. Jaundice diminished and cervical and axillary lymph nodes became smaller. Rectal temperature varied from 98.6° to 99.2°F.

On 12/18/35 whitish papules the size of a pinhead were noticed on arms. X-rays of hands and long bones showed no lesions. On 1/18/26 there was a return of jaundice. 1/30/36: Nonprotein nitrogen of blood 26 mgm. %. Total plasma proteins 6.79 gms. %; albumin 3.53 gms. %; globulin 3.25 gms. %.

He continued to improve slightly. On 3/21/36 the cervical and submaxillary lymph nodes were scarcely palpable; epitrochlears were not felt; axillaries small; inguinals slightly enlarged; femorals still very large, firm, readily movable but not tender.

Histological examination of lymph nodes showed the glands well preserved, but containing many miliary collections of epithelioid cells, scattered singly or arranged in strands and circles. These palely staining "epithelioid tubercles" stood out in sharp contrast to the lymphoid tissue of the node. There were no giant cells and no central areas of necrosis (Fig. 23).

Inoculations were made on Nov. 19, 1935 from the emulsified cervical lymph nodes intraperitoneally into one guinea-pig, into the testicle of one rabbit and intramuscularly into two pigeons. The animals remained healthy until June 24, 1936, when they were sacrificed. At autopsy the lymph nodes, muscles and all organs appeared normal to both gross and microscopical examination.

Summary: A colored man of 28 developed jaundice, abdominal pain and nausea, and a few weeks later contracted a chancre followed by secondary syphilis. He was treated at first intermittently and then continuously with neoarsphenamine and bismuth for over a year. The Wassermann reaction became negative, but during the course of treatment and over a period of one year three subsequent

attacks of jaundice occurred, and one year after the first attack general enlargement of the superficial lymph nodes appeared. There was no fever and no constitutional symptoms other than those accompanying the jaundice, which was followed by loss of weight. The prominent features on physical examination were jaundice and general enlargement of lymph nodes affecting especially the femoral nodes. The liver was enlarged. Radiograms of the chest showed some fibrosis of the lungs; intracutaneous tuberculin reaction negative. No lesions of the bones of the hands could be demonstrated by X-ray. Sections of the lymph nodes showed lesions characteristic of sarcoid, apparently in the early stages of development. Inoculations of the lymph nodes into guinea-pigs, the testicles of rabbits and into pigeons gave negative results.

This case presents certain unusual features. The well marked enlargement of the superficial lymph nodes combined with the recurring attacks of jaundice and the alterations in the lungs, discovered by X-ray, were the predominant signs of disease. Although jaundice is uncommon, it is occasionally mentioned as occurring during the course of generalized sarcoid (Goeckerman). It was important to determine whether the entire syndrome was initiated by syphilis, whether the jaundice was dependent upon the injections of arsphenamine, or whether it was associated with the peculiar disease of the lymph nodes. The first attack of jaundice was said to have occurred before the patient contracted his chancre, and the second attack cleared rapidly after two injections of arsphenamine. There seems, under the circumstances, no grounds for the belief that the patient was suffering from jaundice caused by syphilis or induced by the administration of arsphenamine. Evidence could not be obtained that the jaundice was due to a mechanical cause such as a stone in the common bile duct. It therefore seemed most probable that the symptom was dependent upon an involvement of the liver by "sarcoid," or resulted from pressure by enlarged perihepatic lymph nodes upon the bile ducts. The negative tuberculin reactions and the negative animal inoculations did not furnish any evidence to show that the disease was tuberculous in origin.

Case 7. M. J. a negress, 43 years of age, was admitted to the Johns Hopkins Hospital (Unit no. 67279) on Jan. 30, 1936 for study. She had come out of curiosity to ask about the swellings on her fingers. There was nothing of importance in the family history. She had had measles, mumps, chickenpox and typhoid fever in childhood; pneumonia at 20. An operation for "pus tubes" had been

performed at 29. As an adult she had been very healthy and had worked on a farm. She had been married 17 years.

About five years before admission swellings appeared about interphalangeal joints of hands; they involved first one finger after another until all fingers of both hands were affected. They reached their maximum two or three years before admission, and had not increased since then. They were painless and did not interfere with her work until, within the year, the tips became tender, and sensation for fine touch was impaired. No change in feeling was noticed for heat or cold. About two years ago she noticed nodule at outer angle of left eye, which had increased a little in size. Within last three to four months swellings appeared on upper eyelids. Recently she had noticed that her nose was enlarged. There had been no fever; no loss of weight or strength; no cough and no dyspnoea.

She was a well developed negress; color of the mucous membranes good. On both eyelids, particularly towards inner canthi there were waxy nodules, a few millimeters in diameter, with dry surfaces. Right lachrymal gland seemed swollen. Conjunctivae and corneae appeared normal. On margins of ears there were small nodules, like those on the eyelids, which the patient had not noticed. The end of the nose was bulbous, enlarged and firm; skin was smooth and reddened, and sharply defined from the more normal portion above (Fig. 24). It was not tender. Minute pale nodules formed beads along alae nasi. Nasal mucosa was swollen, reddened and covered with whitish discharge. There was no ulceration of skin or mucous membranes. Tongue, buccal mucosa and throat appeared normal. The few remaining teeth were carious and abscesses were obvious, discharging through the gum. Right pre-auricular lymph node was the size of a pea. Cervical lymph nodes were not palpable. Retromanubrial dulness was not increased. Lungs were clear to auscultation and percussion. Cardiac dulness not enlarged, heart sounds not remarkable. Blood pressure 170/110. There was a ventral hernia through scar of old abdominal incision. Liver and spleen not palpable. The hands presented an extraordinary appearance. There were irregular, symmetrical bulbous swellings about the interphalangeal joints, giving the fingers a gnarled appearance (Fig. 25). Some of the nodules were hard and freely movable; others, particularly on the thumbs, were soft and rubbery. None of them was painful; none showed ulceration. Tips of the fingers were dry, nails were small and dry and some of the terminal phalanges appeared atrophied. In spite of this mutilation there was little pain in tips of fingers. Except for fingers, hands seemed unaffected. Feet showed little change. The phalanges appeared enlarged, the skin thickened, but there were no nodules such as were seen on the hands. There was no oedema of the extremities. X-rays of the chest showed some widening of the arch of the aorta, with two small dense shadows in right lung and rather pronounced shadows at right root. X-rays of the hands showed mutilation of the middle fingers and of the terminal phalanges (Fig. 26). There were irregular areas of rarefaction combined with increased density of bone in shafts of phalanges. In second phalanx of left middle finger there was a punched-out area. There was no thickening of the periosteum or changes in joints. The

bones of the feet appeared normal. Hb. 98%; red blood cells 4,720,000, leucocytes 3,580; polymorphonuclears 72%. Wassermann positive. Non-protein nitrogen of blood 36 mgs. %. Total plasma proteins 6.59 grams %. Albumin 3.49 grams %. Globulin 3.09 grams %. The urine was clear, sp. gr. 1018; acid, no sugar, no albumin. Sediment showed no abnormal elements. 1/17 to 1/29/36 intracutaneous reactions to tuberculin O.T. negative up to 10.0 mg. No acid-fast bacilli found in sputum. Questionable acid-fast bacilli found in single smear from nasal mucosa not confirmed in repeated examinations. 1/22: Excision of nodule on third finger of right hand. 2/6: Agglutination with Brucella melitensis negative. 2/14: Leucocytes 4,280; polymorphonuclears 63%; eosinophiles 2%; myelocytes 2%; lymphocytes 26%; monocytes 7%. 2/21: Blood pressure 128/76. 1/22 and 2/13 inoculation of animals with scrapings from nasal mucosa. During observation the temperature remained normal. 2/21: Intravenous injections of neoarsphenamine started and ultraviolet light used on hands. Within a few weeks hands had definitely improved in appearance, and in June, 3½ months after treatment was begun, the nodules on the phalanges had diminished so much in size that they were scarcely noticeable and swelling of the nose and nasal mucosa had subsided to a considerable extent. Lesions on the ears had healed. Those on the eyelids remained unchanged.

Microscopical sections from the nodule removed from the finger showed a collection of miliary bodies, composed of pale epithelioid cells, between which strands of connective tissue were often seen. There were a few pale giant cells, no areas of necrosis, but occasionally hyaline material. The miliary bodies were separated by connective tissue (Fig. 27).

Inoculations were made on Feb. 13, 1936 with emulsified scrapings from the nasal mucosa intraperitoneally into one guinea-pig and intratesticularly into one rabbit. The guinea-pig died on Mar. 6, 1936, 22 days after inoculation. The lymph nodes and organs showed no tuberculosis. The rabbit remained healthy until it was sacrificed June 24, 1936, over 5 months after inoculation. The testicles, lymph nodes and organs appeared normal to both gross and microscopical examination.

Summary: A negress 43 years of age, with a positive Wassermann, with gradual formation over five years of nodules on fingers, later deformity and practically painless mutilation of fingers, appearance of minute nodules on eyelids and ears and swelling of nose and nasal mucosa. The disease progressed without constitutional symptoms. X-rays of the hands showed changes in shafts of phalanges without involvement of periosteum or joints. Tuberculin reaction negative; animal inoculations of scrapings from nasal mucosa negative. Gradual improvement after treatment with neoarsphenamine and exposure to ultraviolet light.

This patient presents a common form of the disease in which there is a combination of involvement of the nose and nasal mucosa in a process designated as "Lupus pernio" with extensive disease of the

phalanges of both hands. The enlargement of lymph nodes was insignificant, and it is questionable whether the shadows in the right lung, observed in the X-ray, formed a part of the disease. The lack of constitutional symptoms was striking and it was remarkable that the patient could use her deformed and mutilated hands for cooking and for her work on the farm. The suspicion was at first aroused that the patient had leprosy, and the report that bacilli had been found in the scrapings from the nasal mucosa which were not completely decolorized by acid seemed to lend support to this suggestion. The fact that this observation could not be confirmed, and that the microscopical appearance of the nodule from the finger appeared quite characteristic of sarcoid, led to the conclusion that the condition was Boeck's sarcoid. There was no evidence of tuberculosis. The intracutaneous tuberculin reaction was negative to 10.0 mg. of O.T.; acid-fast bacilli could not be found in the sputum, and the inoculations of animals with material from the nose gave negative results. The marked and comparatively rapid improvement that followed the administration of neoarsphenamine and the use of ultraviolet light was striking.

Case 8. R. H., a negro, 36 years of age, was transferred from the Wilmer Clinic to the Osler Clinic of the Johns Hopkins Hospital on May 7, 1936 for further study (Unit no. 70775). His mother and father had died of unknown causes. No known tuberculosis in the family. He had had measles at 10; influenza and pneumonia at 18; gonorrhoea and chancre at 27 (1927), and a positive blood test 4 years later (1931). Married 11 years. Wife had had one miscarriage; one child dead at 9 months. General health good until three years ago when his eyes began to trouble him. In Nov. 1933 there was photophobia and lachrymation. In Mar., 1934, there was found in Wilmer Clinic pericorneal congestion, haziness with old exudates on right cornea and iris bombé; numerous deposits seen on posterior corneal surface. Pupils oval and inactive; left cornea clearer than right; tension normal. Diagnosis of iridocyclitis with secondary glaucoma was made. In Apr. 1934 he was seen in the Syphilis Clinic. He was described as small but well nourished, with bowed tibiae, prominent frontal bosses, normal hearing, generalized macular eruption over entire body and enlargement of all superficial lymph nodes. Lungs and heart appeared normal; B.P. 110/84; spleen and liver not felt. Epididymes enlarged, firm and tender; deep reflexes present and active. Wassermann positive. From Apr. 13, 1934 to July 10, 1935, he was treated alternately with neoarsphenamine, silver arsphenamine and "Bismogenal." Early in May 1934 blood Wassermann became negative. There was gradual improvement in the condition of eyes, although in Feb. 1935 there were

still deposits on cornea with marked aqueous ray. In May 1935 he had epistaxis with evidence of bismuth stomatitis. In Nov. 1935, there was mild conjunctivitis of left eye; aqueous ray was negative and corneae clear. In Jan. 1936, small firm nodular masses were noted beneath eyelids, with pericorneal injection on left, clouding of cornea and immobile and irregular pupil. At this time one of the tumors was removed from beneath the left upper eyelid. From the microscopical examination the diagnosis of Boeck's sarcoid was made. In Mar. 1936 a cough, which the patient had had for some time, increased in severity. He had night sweats, pain in chest and lost weight. He expectorated foul-smelling sputum. The intracutaneous reaction was positive with 1 mg. of O.T. tuberculin but negative with smaller doses. On Apr. 23, 1936 he was admitted to the Wilmer Clinic with a history of general malaise, feverishness, loss of appetite, cough and sputum for about two weeks. Temperature on admission 100°F. There were signs of solidification of right lower lung anteriorly with many râles, and dulness with râles at angle of right scapula. X-ray showed infiltration in the right lung. Leucocytes 7,000. There was some cough, but very little sputum. For two weeks temperature varied between 99° and 103° with daily exacerbations. Later there was general improvement.

On admission to Medical Service, May 7, 1936, temperature was 101.8°, pulse 90, respirations 24, blood pressure 94/64. He was thin, did not seem very ill, had no cough, dyspnoea or cyanosis. There was pallor with scaling papules on left arm and general enlargement of lymph nodes, particularly of epitrochlears. The largest were the size of beans. All nodes were discrete, rubbery and lacked tenderness. Marked bosses on forehead. Right eyeball had been practically destroyed and supraorbital ridge bulged. Scars were seen on eyelid and lachrymal gland was visible. There was moderate vision in left eye with hazy media and scar on left upper eyelid. Parotid glands not definitely enlarged, but small, hard, irregular nodules, either in or above the parotid, were present in both pre-auricular regions. There was no tenderness. Hands, wrists and feet appeared normal. X-rays of hands and feet showed no abnormalities. Chest was long, respiratory movements were limited. Anteriorly, lungs were resonant with sibilant râles on right. Posteriorly, there was dulness in right interscapular space and over right scapula. Breath sounds were bronchovesicular over area of dulness with tubular whisper and subcrepitant râles after cough. In left interspace there was exaggerated broncho-vesicular respiration and sibilant râles. Heart not enlarged. P.M.I. in 5th space 8 cm. from midline; dulness in 5th space 8.5 cm. from midline. Sounds clear. Abdomen flat. Liver not felt. Spleen readily palpable 2 cm. below costal margin. Both testicles were firm; epididymes enlarged, irregular and firm. There were saber shins. Hb. 60%; red blood cells 4,010,000; leucocytes 8,120; polymorphonuclears 81%; myelocytes 2%; lymphocytes 13%; monocytes 3%; basophiles 1%. Wassermann negative. Urine: acid, sp. gr. 1011–1020; no sugar; no albumin; microscopically, a few leucocytes. No acid-fast bacilli seen in smears from nasal mucosa or in repeated examinations of the sputa. May 8, 1936, X-rays of lungs showed lobular masses to right and

left of mediastinum, with infiltration of lungs at roots (Fig. 28). No changes were seen in bones of orbits. Temperature gradually fell to normal by May 12 and thereafter only occasionally reached 100° by rectum until May 27, when patient had shaking chill, sudden rise of temperature to 104°, with headache, pain beneath right scapula, cough, sputum and showers of râles at right apex posteriorly. Sputum showed group IV pneumococci. On next day, May 28, temperature was normal and patient felt perfectly well. There was gradual symptomatic improvement with gain in weight. He continued to improve symptomatically and in January, 1937 stated that he felt well. Swelling of left lachrymal gland had almost disappeared; nodules in parotid glands small; physical signs in chest and X-ray unchanged.

Sections of excised lymph node showed its structure partially preserved but studded with miliary collections of large pale epithelioid cells, without reaction about them. Central giant cells were rare. Occasionally pale vacuolated granular areas were seen in the centres of the tubercle-like bodies. Sections of a nodule over parotid region showed well preserved tissue of the parotid gland. In places there were miliary collections of epithelioid cells similar to those in the lymph node (Fig. 29). Elsewhere epithelioid cells infiltrated the gland in a more diffuse manner, obliterating much of the gland tissue. Near these portions the tissue was invaded by lymphoid cells, plasma cells and a few polymorphonuclear leucocytes.

Summary: A colored man 36 years of age developed syphilis and six years later bilateral iridocyclitis, followed by general glandular enlargement, unaffected by prolonged antisyphilitic treatment. Nodules appeared later beneath eyelids and in parotid glands. Subsequently there was involvement of the lungs, with fever, cough, and sputum, from which he gradually improved. No tubercle bacilli in sputum; intracutaneous tuberculin reaction positive only with 1 mg. O.T. Sections of lymph node and parotid gland showed lesions of Boeck's sarcoid.

This case presented a much more complicated problem than any of the preceding ones. It was at first thought by the ophthalmologists that the bilateral iridocyclitis was due to syphilis, but the continuation of the process under intensive antisyphilitic treatment with prompt reversion of the Wassermann reaction to negative, led to the conclusion that the condition was not syphilitic in origin. When, later, signs of extensive disease of the lungs appeared, it was concluded that the patient had pulmonary tuberculosis with iridocyclitis, lymphadenitis and probable involvement of the parotid glands. The lack of conclusive proof of tuberculosis, and an examination of the sections from the nodule under the left upper eyelid, the lymph node and the parotid gland, resulted finally in the suggestion that the

syndrome should be classified as an example of generalized sarcoid. The characteristic lesions of the skin and bones were not observed. In some respects, however, the course of the disease resembled that described in uveoparotid fever. There was not, however, a history of acute swelling of the parotid glands in this patient and there were never any evidences of paralysis of the cranial nerves.

DISCUSSION

In reviewing the clinical pictures presented by these eight patients one is immediately struck by the widespread and protean nature of the disease. It is probably a coincidence that the eight patients were all negroes, for only two of the nine patients from the Pennsylvania Hospital were of this race, and the vast majority of the cases reported in the literature have been in white patients. Ten of the eighteen patients were between the ages of 20 and 43; one patient was 80 years of age and the remaining 7 were between the ages of 10 and 20. The disease is recorded as being most common between the ages of 20 and 40.

The onset of the disease was usually insidious, and one of the remarkable features was the paucity of constitutional symptoms, even when the pathological changes had progressed to a stage in which the skin, the lymph nodes, the lungs, or the bones of the hands had become extensively involved. Pain rarely accompanied the enlargement of the lymph nodes or the extraordinary changes in the hands. Some loss of weight was occasionally recorded, but fever was observed only in four of the eight cases (cases 1; 4; 5; 8) (Table I), and in each of these patients there was more or less extensive involvement of the lungs or mediastinum. In only one (case 8), however, did the elevations in temperature exceed 101° by rectum, and even with quite extensive changes in the lungs and mediastinum the increase in temperature was in some instances insignificant (case 1) or fever was entirely absent (case 3). One of these latter patients (case 1) complained of dyspnoea. Cough and expectoration occurred in only two of the five patients who presented signs of disease of the lung and mediastinum. One patient in whom the larynx was affected complained of hoarseness (case 4).

Two patients (cases 5 and 6) developed jaundice during the course

TABLE 1

Résumé of the principle clinical features in eight cases of sarcoid

CASE No.	CASE Pt.	AGE	COLOR	SEX	SKIN	SUPERF. L. N.	MEDIAST. BRONCH. L. N.	LUNG	SPLEEN	LIVER	BONES	FEVER	OTHER TISSUES INVOLVED	COMPLICATIONS	RESULT
1	E. W.	38	C	F	0	++++	++	++	0	+	0	0		Dyspnoea	Unchanged
2	T. M.	14	C	M	0	++++	?	0	0	0	0	0	Lachrymal and parotid		
		18			++++	++	±	+	−	−	+++	±		Syph. Wass. +	
		24			+	0	0	0	0	0	++	0		Wass. 0	Well?
3	R. G.	24	C	F	0	++++	++++	+++	0	0	0	0			
		34			0	0	0	0	0	0	0	0			Well
4	V. G.	21	C	F	+++	+++	+	++	+	0	++++	±	Nasal mucosa, larynx		Unknown
5	S. H.	18	C	M	0	+++	+++	++	0	0	0	+	Muscles of arms	Dyspnoea	
		19½			0	+	−	++	−	−	−	−	Nodules disappeared	Cough Jaundice Wass. 0	Stationary
6	R. K.	28	C	M	+	+++	0	±	0	+	0	0		History of Syph. Jaundice	Improved
7	M. J.	43	C	F	+++	±	0	0	0	0	++++	0	Nasal mucosa. Lachrymal gland	Syph. Wass. +	Improved
8	R. H.	36	C	M	0	++	++	++++	+	0	0	++	Iridocyclitis, lachrymal and parotid		Improved

of the disease, and in one (case 6) this recurred in four separate attacks. In one patient (case 2) the onset of the disease was preceded by what was supposed to be an attack of mumps, and in one patient (case 8) the disease probably began with an involvement of the uveal tract. The slowly progressive nature of the process is illustrated by the course of the disease in case 2 in which it persisted for ten years, and in cases 4 and 7 in which there was a gradual and almost asymptomatic progression of the disease to an advanced stage, affecting many organs and particularly the bones over periods of 4 and 5 years, respectively.

The one constant feature which was present in all of our patients and which often assumed a prominence over all other signs was a noticeable enlargement of the lymph nodes. Usually all the superficial lymph nodes were more or less swollen, but in many instances the enlargement of certain groups attracted particular attention. The pre-auricular, postauricular, submaxillary and submental nodes were frequently very conspicuous, while in some instances the prominence of the epitrocheal nodes was especially obvious. In one instance the femoral nodes were very large (case 6). The mediastinal nodes appeared as tumor masses in the radiograms from cases 1, 3, and 5. It was noticeable in some instances that the lymph nodes in the anterior cervical chains, in the supraclavicular regions and in the axillae, were comparatively small. A characteristic of all the enlarged nodes was that they were smooth, rubbery, or firm, discrete, freely movable, and that they were not tender. They resembled almost exactly the glandular enlargements in Hodgkin's disease, although they never reached any great size. The similarity was sufficiently close, however, to lead to the clinical diagnosis of Hodgkin's disease in 3 of the 8 cases.

Though enlargement of the lymph nodes has been repeatedly recorded in the literature, even in patients in whom the disease seemed to be limited to the skin, very little emphasis has been placed on this feature. In view of the fact that the presence of glandular enlargement has been so common in our patients and has been so prominent in some of them, it becomes necessary to direct attention to this phase of the disease.

So much has been written about the dermatological lesions that

it is only desirable to reiterate the fact that the disease is often seen without abnormalities in the skin. In only four of our 8 cases was the skin affected. Two of these four patients presented the picture of "lupus pernio."

In addition to the skin the mucous membranes were occasionally affected. In cases 4 and 7 the mucosa of the nose was swollen and reddened and in case 4 the larynx was involved in the same way.

The pulmonary lesions were remarkable on several accounts. With more thorough study of these patients abnormalities of the lungs are found in a constantly increasing proportion. Definite changes in the mediastinum or lungs were demonstrated either by physical signs or by X-ray in seven of these eight patients. Fever of mild degree seems to accompany these changes in many instances, for it was present in four of the seven cases. But the changes may reach considerable proportions without producing localizing symptoms and without causing more than minimal signs, in comparison to the extent to which the lungs are invaded. This was especially true in cases 1 and 3. Since the changes are most marked at the roots and in the superior mediastinum, the abnormal physical signs are usually detected in the interscapular spaces and in the region of the manubrium. Dulness and tubular modification of the breath sounds or of the whispered voice occurred more frequently than râles. The radiographic shadows, which are often quite dense, were seen extending from the roots of the lungs towards the bases. The filmy, lace-like shadows clouding the lower lobes, and seen very clearly in case 3, have frequently been described and in some instances have been mistaken for miliary tuberculosis or for the changes induced by some occupational disease. The shadows in the superior mediastinum often resemble, as they did in Case 3 and Case 5, those cast by the enlarged glands in Hodgkin's disease or lymphosarcoma.

The lesions in the bones seem to be almost specific. Nothing can be added to the excellent and elaborate description which Jüngling has given of these changes. They occurred in three of the eight cases in typical form, and are illustrated in Cases 2, 4, and 7. They most commonly attack the phalanges of the hands and feet, and the metacarpal and metatarsal bones. In these situations they may be combined with symmetrical nodular swellings about the interphalangeal

joints (Cases 4 and 7). Even with the most advanced lesions in the shafts of the bones there was little or no pain and the movements of the fingers were surprisingly well preserved. The explanation for this is probably due to the fact that the disease does not invade the periosteum and does not involve the joints. In Case 4 the disease was not confined to the fingers and toes but had spread to the tarsal bones and to the long bones of the arms. Such a widespread affection of the bones is very unusual.

The liver was enlarged in Cases 1 and 6, and the spleen was readily palpable in Cases 4 and 8, but it is impossible to determine whether the enlargement of these organs was due to the invasion of the tissues by sarcoid or was produced in some other way.

The lachrymal glands appeared to be involved in two instances (Cases 2 and 8) and the parotid gland was definitely invaded in Case 8. The epididymes were enlarged and firm in Cases 5 and 8, but the chronic epididymitis might readily have been caused by previous gonococcal infections.

An examination of the blood in these eight cases did not show with any regularity significant deviations from normal. In Cases 3, 4 and 8 there was a very slight anaemia, the Hgb. being 70%, 61% and 60%, and the red blood cells 4.5, 3.7, and 4.0 million, respectively. In the remaining five cases the Hgb. varied between 80% and 100% and the red blood cells between 4.3 and 5.3 million. In one case (Case 6) the leucocyte count was 11,300, but in the other seven it tended to be low, averaging between 3,500 and 8,100. The differential formula was not constantly changed. The polymorphonuclear leucocytes varied in 7 cases between 53% and 71%. In Case 8 they were 83%. Eosinophiles were present in all but one case (8). In one instance (Case 3) there was a striking eosinophilia reaching at one time 35%. In two other cases (5 and 6) the eosinophiles were 7% and 6% respectively, but in the four remaining cases they varied between 2% and 4%. The proportion of small lymphocytes was not remarkably changed. They varied between 13% and 33%. An increase in the monocytes, observed by a few writers, was found in only one instance, Case 5, in which they formed 18% of the leucocytes.

Determination of the plasma proteins was made in three cases (2, 6, and 7). Significant increases, such as those recorded by Salvesen (33), were not found in any of these. The figures were 7.32 grams %;

6.79 grams % and 6.59 grams % respectively. In two instances (cases 6 and 7) there was a slight relative increase in globulin with a corresponding decrease in albumin.

It should be pointed out that none of the patients presented any symptoms or signs that indicated disease of the peripheral or central nervous system.

In spite of this fact the course of the disease in Case 8 resembled in some respects the curious syndrome first designated by Heerfordt (57) as "Febris uveo-parotidea-subchronica." During the last few years this disease has attracted considerable attention. There may be some significance in the fact that many instances of the disease have been reported from Scandinavia, a part of Europe in which sarcoid appears to be quite common. Reports of cases with accounts of the disease and bibliography have been published by Hamburger and Schaffer (58); Tanner and McCurry (59); Nowkirischky (60); and Kruskal and Levitt (61); among many others. In 1933, Garland and Thomson (62) collected and analyzed 47 cases; in the next year Savin (63) found 66 recorded cases and added one of his own, and in 1935, Cohen and Rabinowitz (64) stated that they could find "about 65 cases" in the literature and recorded still another instance.

In brief this syndrome is characterized by bilateral uveitis and parotitis preceded or accompanied at first by fever. Later, as the disease becomes chronic, the fever usually subsides and other symptoms and signs are likely to appear, but eventually, after many months, there is, as a rule, recovery. Paralysis of the facial nerve is said to accompany the swelling of the parotid glands in about one-third of the patients, and in approximately half of these it is bilateral. Pareses of other cranial nerves may occur or more distant parts of the nervous system may be affected. During the course of the disease swelling of the submental, submaxillary and cervical lymph nodes may appear, occasionally cutaneous eruptions of various kinds, including erythema nodosum, are observed, and in a few cases radiograms disclose increased shadows in the mediastinum or at the roots of the lungs. In rare instances the spleen is enlarged. Slight anaemia may develop, and though the total leucocytes may not be increased, an eosinophilia is noted fairly often. Savin states that there have been 5 deaths; Cohen and Rabinowitz found only 3 deaths recorded.

The pathological descriptions and the illustrations of the lesions

in the lymph nodes and parotid glands are almost precisely the same as those so familiar now in sarcoid. The miliary epithelioid tubercle with occasional giant cells but with almost complete absence of necrosis seems to be characteristic of the pathological lesion.

The etiology of the disease has been much disputed. It is considered to be a form of tuberculosis by many writers, for definite tuberculosis has been associated with the syndrome in some instances. Garland and Thomson report a fatal case dying of miliary tuberculosis and record two others from the literature. On the other hand the cutaneous tuberculin reaction is rarely positive. Tubercle bacilli have not so far been found in sections of excised material, and the few inoculation experiments that have been made are said to have been negative (Cohen and Rabinowitz).

Case 8 of our series presented many of the features of uveoparotid fever. The disease started with bilateral uveitis and iridocyclitis. Later there was invasion of the parotid glands with enlargement of the submental and submaxillary lymph nodes, and during the later phase of the illness there were well marked lesions at the roots of the lung accompanied by fever and constitutional symptoms. In Case 2 the first sign of the disease gave the appearance of mumps, an onset that corresponds well with the accounts of the cases of uveoparotid fever.

In the descriptions of uveoparotid fever there are no references to the occurrence of "Lupus pernio," to sarcoid of the skin, or to lesions in the bones, and in this respect the syndrome of uveoparotid fever differs from that of Boeck's sarcoid. The clinical picture of Boeck's sarcoid, however, appears in such a variety of forms, that the close resemblance of the pathological changes which may affect similar tissues in the two syndromes, leads unavoidably to the suggestion that uveoparotid fever may prove to be still another, though very distinctive form, of Boeck's sarcoid. Furthermore, the discussions in the literature concerning the etiology of the two diseases and the connection which tuberculosis bears to this problem are almost identical.[1]

[1] Since the preparation of this manuscript our attention has been called to a paper by Dr. W. J. B. Slot (Nederl. Tijdsrft. voor Geneesk., Jahrg. 80, pp. 2859–2863, 1936), who reports a case of Besnier-Boeck's disease and a case of uveo-

Investigations concerning the etiology of sarcoid in our cases have not led to any positive results (Table II). Intracutaneous tuberculin reactions made in seven cases (Cases 1, 3, 4, 5, 6, 7, 8) were negative in all but one instance with from 0.01 mg. to 10.0 mg. of O.T. In Case 3 the reaction was negative to 0.1 mg. but mildly positive with 1.0 mg. In the same patient 0.1 mg. of avian tuberculin gave a negative intracutaneous reaction, while 1.0 mg. of avian tuberculin gave a mild positive reaction. In Case 8 the intracutaneous tuberculin reaction was positive only with 1.0 mg. of O.T.

TABLE 2

Results of tuberculin reactions and bacteriological studies in eight cases of sarcoid

CASE		TUBERCULIN REACTION				SECTIONS FOR ACID-FAST BACILLI	MATERIAL	INOCULATIONS			
No.	Pt.	O.T.		Avian				Culture	Guinea-pig	RABBIT	PIGEON
		+	0	+	0						
		mg.	*mg.*	*mg.*	*mg.*						
2	T. M.					0	Lymph nodes	0	0		
3	R. G.	1.0?	0.1	1.0?	0.1	0	Lymph nodes	0	0	0	0
4	V. G.		0.5			0	Lymph nodes	0	0	0	0
5	S. H.		1.0			0	Lymph nodes Muscle	0 0	0 0		
6	R. K.		0.1			0	Lymph node		0	0	0
7	M. J.		10.0				Nasal mucosa	0	0	0	
8	R. H.	1.0	0.1			0					
9	City Hosp.						Lymph node	0	0	0	0

Acid-fast bacilli could not be found in the sections of lymph nodes from any of the cases. Cultures from the lymph nodes on Dorset Egg medium made by Dr. Willis from Cases 2, 3 and 9[2] gave no growth. Cultures from the lymph nodes, skin nodule and nasal mucosa on Sabouroud's medium were made from Case 4 with negative results.

parotid fever. The first case, diagnosed as Besnier-Boeck's disease, was that of a woman showing conjunctivitis, parotitis, rhinitis and enlargement of the bronchial lymph nodes, marbleization of the lungs and an erythrodermic type of Boeck's lupoids. The second case, diagnosed as uveoparotid fever, was that of a young man with bilateral subchronic parotitis, iridocyclitis and edema of the legs. Slot suggests that the two diseases are one and the same and should be considered as due to atypical tuberculosis.

[2] Patient seen with Dr. Boggs at City Hospital.

Inoculation of material from the lymph nodes from 6 cases (2, 3, 4, 6 and 9) and from the nasal scrapings from one case (7) were made into guinea pigs with entirely negative results. Similarly, inoculations of material from lymph nodes in 3 cases (3, 6, and 9) and of the nasal scrapings from one case (7) were made into rabbits, in two instances (Cases 6 and 7) intratesticularly, with negative results. Finally inoculation of material from the lymph nodes from four cases (Cases 3, 4, 6 and 9) into pigeons gave negative results. Although these observations and experiments may not exclude the different types of the tubercle bacillus from participation in the disease, they do not lend the slightest support to the idea that the disease represents a form of tuberculosis.

Sections of lymph nodes from 7 cases were stained and searched for Leishman-Donovan bodies, but none was found. The serum from Cases 6 and 7 did not agglutinate Br. abortus or Br. melitensis.

A history of syphilis or a positive Wassermann reaction was obtained in only three of the eight cases (Cases 6, 7 and 8), which for negroes is not a high percentage.

Unfortunately, it has not been possible to repeat the interesting observations of Williams and Nickerson (52), for all the patients who came under our observation after the publication of their paper have had syphilis, but if their observations are confirmed, it might eventually prove that the disease is due, as they suggest, to a virus.

There are, on the other hand, some characters, such as the changes in the bones, that have led to the supposition, particularly by Kissmeyer and by Nielsen, that Boeck's sarcoid is closely related to leprosy. No direct evidence has been forthcoming to substantiate this interesting conception.

From many points of view Boeck's sarcoid holds a position somewhat analogous to Hodgkin's disease, and indeed by some it has been termed "Benign lymphogranuloma." The analogy is particularly close as regards the discussions concerning the relationship of the two conditions to tuberculosis.

At the present time one can only conclude that the cause of Boeck's sarcoid is unknown.

Treatment has been entirely empirical. Most of our patients have been exposed to ultraviolet light, and several have been given neo-

arsphenamine intravenously, but it cannot be said that these methods have had any material effect upon the course of the disease. In Case 3 complete recovery followed the use of ultraviolet light alone. During the same form of therapy the lymph nodes subsided gradually in Case 2, but many years later lesions of the bones became manifest. There was comparatively rapid improvement in the condition of the skin lesions and of the nodular swellings about the fingers in Case 7 during a course of injections of neoarsphenamine combined with exposure to ultraviolet light. It is quite possible, however, that the improvement in the condition of these patients was spontaneous and was not attributable to the therapeutic measures that were employed.

SUMMARY

Eight cases of generalized Boeck's sarcoid are described, and reference is made to an enlargement of the lymph nodes that occurred in ten additional patients.

The disease pursued the course of a chronic generalized infection, producing few constitutional symptoms but resulting in remarkable pathological changes in many structures of the body.

Although the condition has been most often described as a disease of the skin, characteristic changes in the skin were only observed in four of our cases.

Emphasis is placed on the generalized nature of the process and the frequency with which an enlargement of particular groups of lymph nodes occurs in this disease. Those most commonly involved are the pre-auricular and postauricular, the submaxillary and submental, the epitrochlear and the femoral or inguinal nodes. One or more of these groups was enlarged in all cases.

Involvement of the roots of the lungs or of the mediastinum is also quite common and was observed in 7 of our cases. The changes produced somewhat characteristic shadows in the radiogram.

The alterations in the small bones of the hands and the feet, usually affecting the phalanges, seem to be specific for this disease. They produce perfectly typical shadows in the radiogram. Disease of the bones occurred in three of our patients and in one case they were unusually widespread. In two cases the spleen and in two the liver was enlarged. The lachrymal glands were swollen in two instances,

the parotid gland was involved in one patient. Bilateral iridocyclitis occurred in one patient.

Reference is made to the resemblance of some of the clinical features of uveoparotid fever to Boeck's sarcoid, and attention is drawn to the close similarity of the pathological lesions in the two syndromes.

The pathological picture of Boeck's sarcoid reproduces almost exactly the miliary epithelioid tubercle without a surrounding inflammatory zone. Large pale central giant cells are sometimes seen, but areas of necrosis are exceptionally rare.

The *etiology* of Boeck's sarcoid remains as yet undetermined. The disease is considered by many to be a peculiar form of tuberculosis. The tuberculin reaction is positive in only a small proportion of cases. It was mildly positive in one of 7 of our patients. In one case (No. 2) a tuberculin reaction was not made. In the cases of this series in which cultures were made from the lymph nodes, and in which guinea-pigs, rabbits and pigeons were inoculated with material from the lymph nodes and from nasal scrapings, the results were all negative.

Up to the present time the efforts of most investigators to prove that the disease is tuberculosis have failed and one must conclude that the etiology of the disease remains unknown.

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FIG. 1. CASE 1. E. W. SHOWING ENLARGEMENT OF PRE-AURICULAR, SUBMAXILLARY AND SUBMENTAL LYMPH NODES

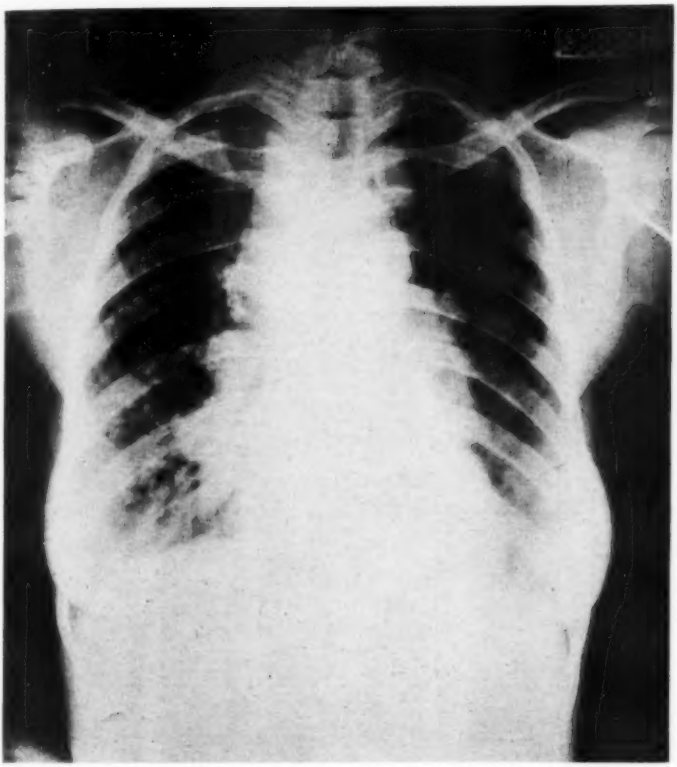

FIG. 2. CASE 1. E. W. ROENTGENOGRAM OF THE CHEST, SHOWING ENLARGEMENT OF SUPERIOR MEDIASTINAL AND PERIBRONCHIAL LYMPH NODES, WITH INCREASED DENSITY OF ROOT SHADOWS AND RETICULATED FINE MOTTLING OF LOWER RIGHT CHEST

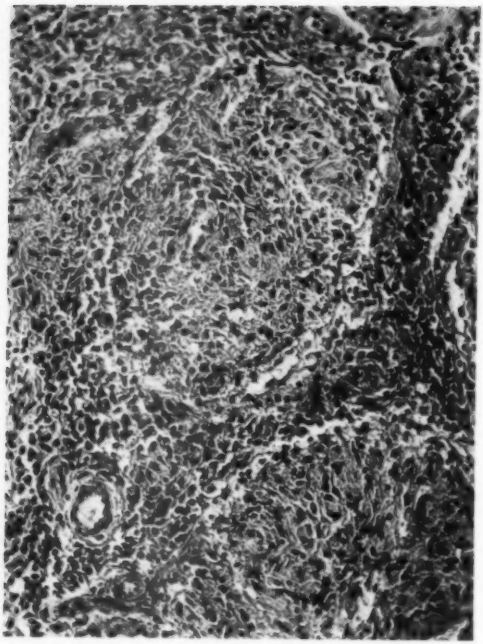

FIG. 3. CASE 1. E. W. SECTION OF LYMPH NODE SHOWING EPITHELIOID "TUBERCLES"

FIG. 4. CASE 2. T. M. APPEARANCE OF PATIENT AT AGE OF 14, IN 1926

FIG. 5. CASE 2. T. M. SHOWING ERUPTION ON FACE IN 1930

FIG. 6. CASE 2. T. M. SHOWING BULBOUS SWELLING OF FINGERS IN 1930

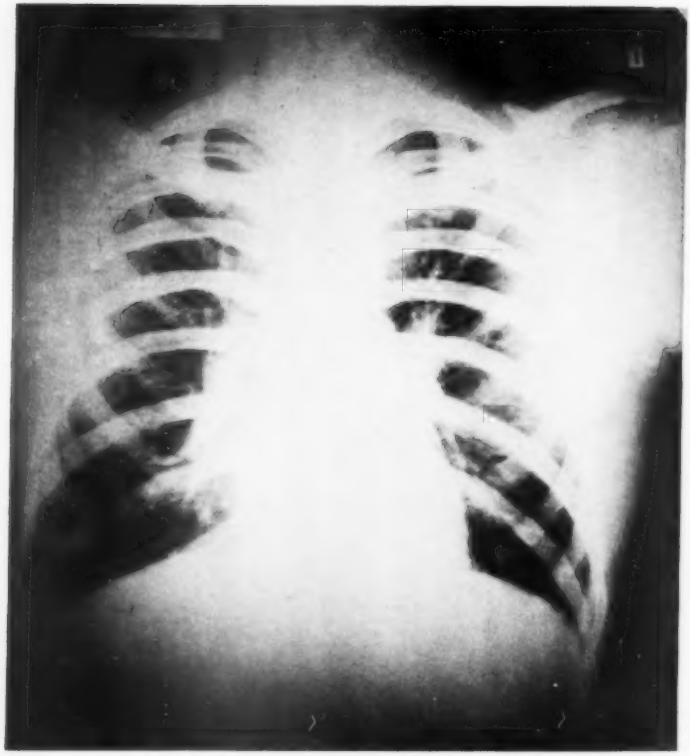

FIG. 7. CASE 2. T. M. ROENTGENOGRAM OF CHEST SHOWING INCREASED ROOT SHADOWS EXTENDING PARTICULARLY INTO RIGHT LUNG IN 1930

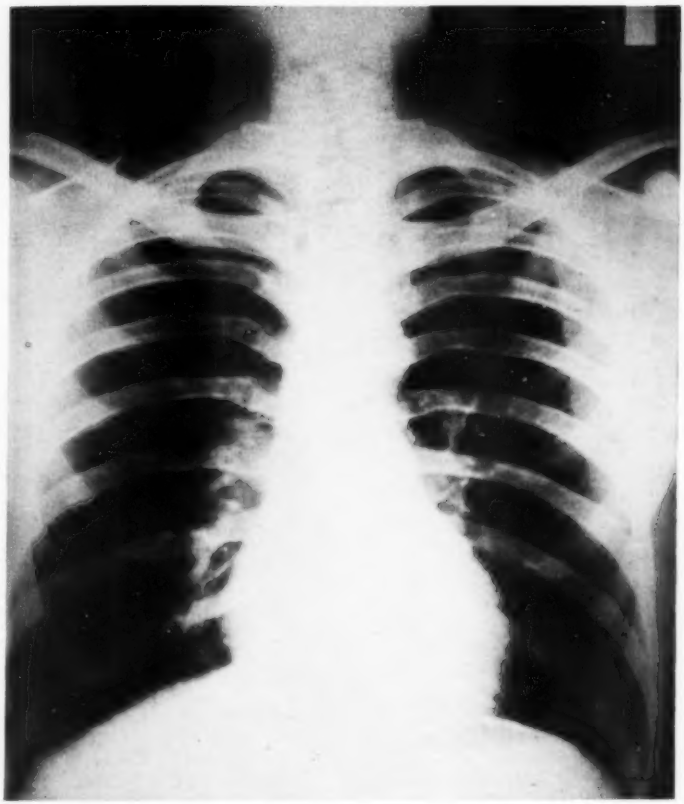

FIG. 8. CASE 2. T. M. ROENTGENOGRAM OF CHEST IN 1936 SHOWING COMPLETE DISAPPEARANCE OF SHADOWS PRESENT IN 1930

FIG. 9. CASE 2. T. M. APPEARANCE OF PATIENT IN 1936
Note stubby fingers with squaring of terminal phalanges

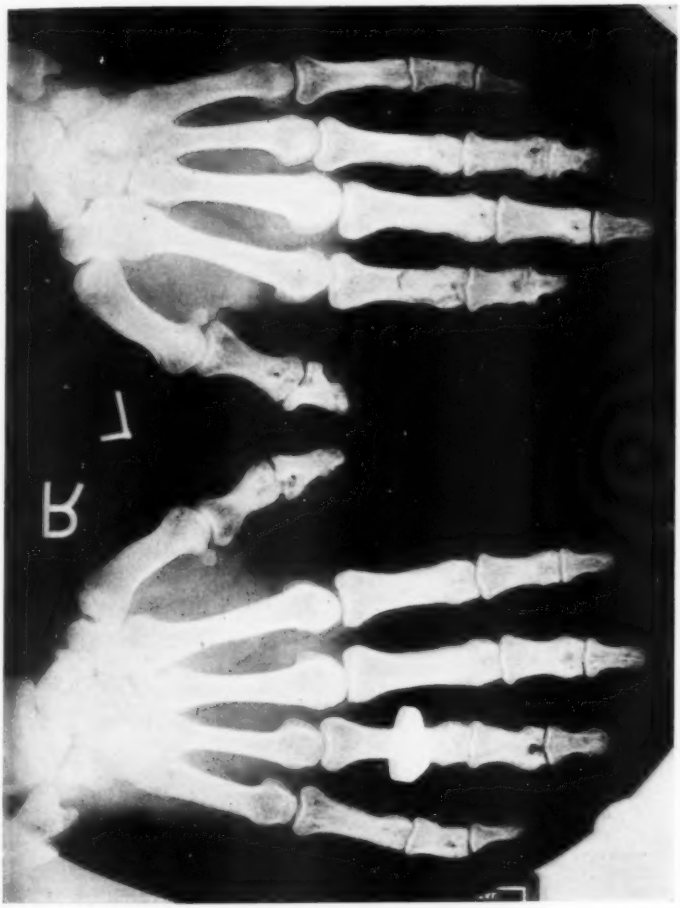

FIG. 10. CASE 2. T. M. RADIOGRAM OF HANDS, SHOWN IN FIGURE 9

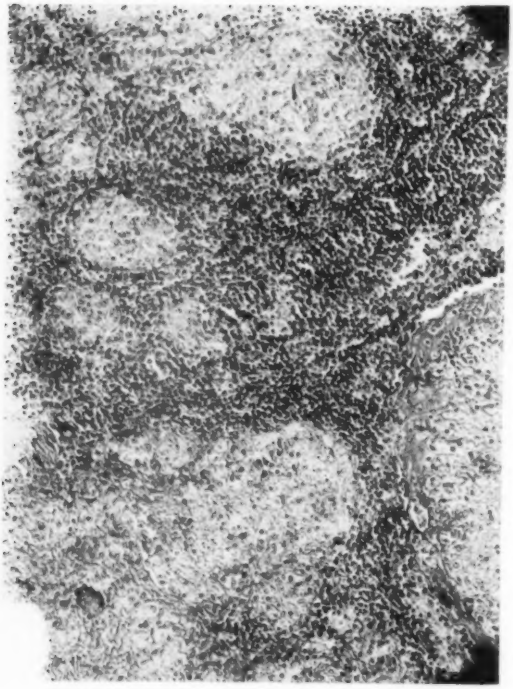

FIG. 11. CASE 2. T. M. SECTION OF LYMPH NODE REMOVED FROM PATIENT IN 1926, SHOWING NUMEROUS EPITHELIOID "TUBERCLES" WITH ONE LARGE GIANT CELL

FIG. 12. CASE 3. R. G. APPEARANCE OF PATIENT IN 1926, SHOWING COLLAR OF ENLARGED LYMPH NODES ABOUT THE JAWS

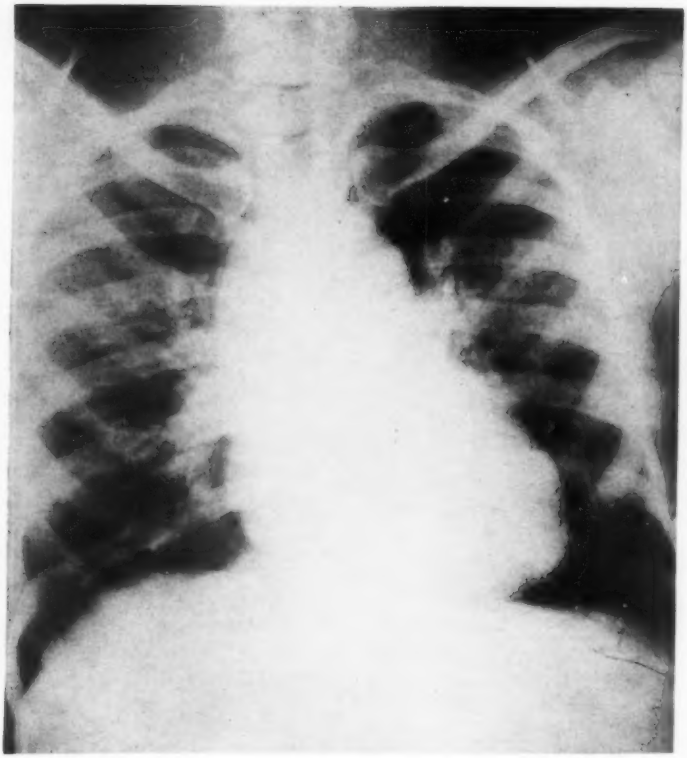

FIG. 13. CASE 3. R. G. RADIOGRAM OF CHEST IN 1926 SHOWING ENLARGEMENT OF SUPERIOR MEDIASTINAL LYMPH NODES AND INFILTRATION AT ROOTS OF LUNGS

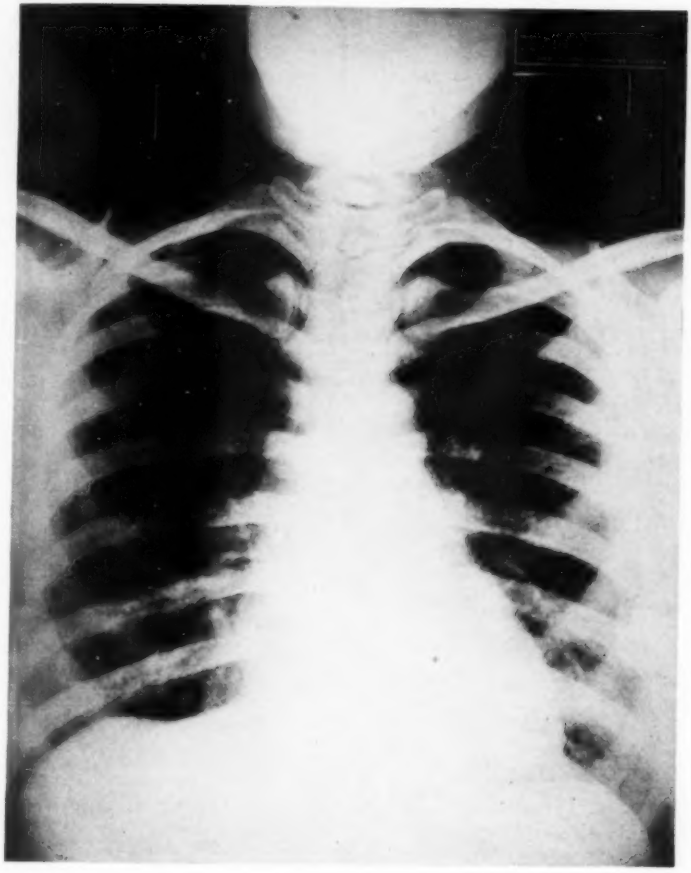

FIG. 14. CASE 3. R. G. RADIOGRAM OF CHEST MADE IN 1936, TEN YEARS AFTER THAT SHOWN IN FIGURE 13, SHOWING DISAPPEARANCE OF MEDIASTINAL SHADOW AND CLEARING OF LUNG FIELDS

FIG. 15. CASE 4. V. G. SHOWING SWELLING OF NOSE AND ERUPTION OF NODULES ON FACE

FIG. 16. CASE 4. V. G. SHOWING ENLARGEMENT ABOUT WRISTS AND NODULES ABOUT INTERPHALANGEAL JOINTS, WITH LONGITUDINAL STRIATIONS ON NAILS

FIG. 17. CASE 4. V. G. RADIOGRAM OF HAND SHOWING LACE-LIKE RAREFACTION OF PHALANGES, METACARPALS, CARPALS, RADIUS AND ULNA

FIG. 18. CASE 4. V. G. RADIOGRAM OF FOOT, SHOWING LESIONS SIMILAR TO THOSE SHOWN IN FIGURE 17, WITH TWO PUNCHED-OUT AREAS IN PHALANGES

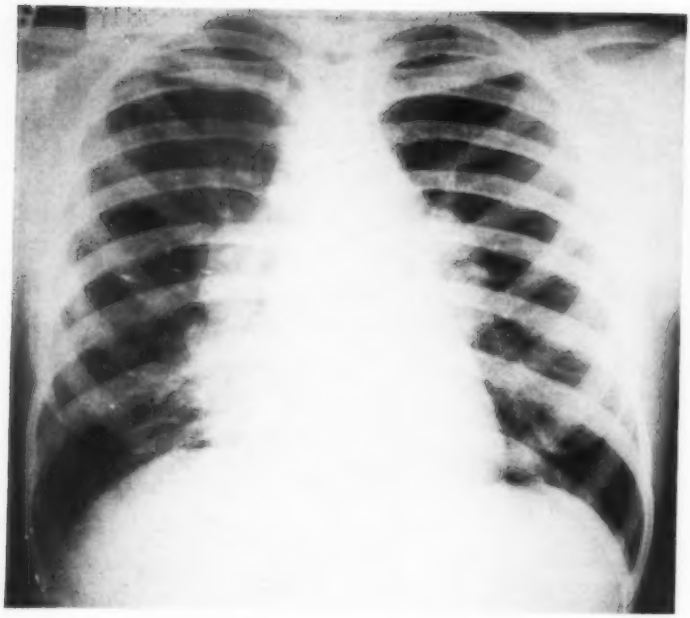

FIG. 19. CASE 4. V. G. RADIOGRAM OF CHEST SHOWING ENLARGED BRONCHIAL LYMPH NODES WITH SHADOWS EXTENDING TO THE BASE IN RIGHT CHEST

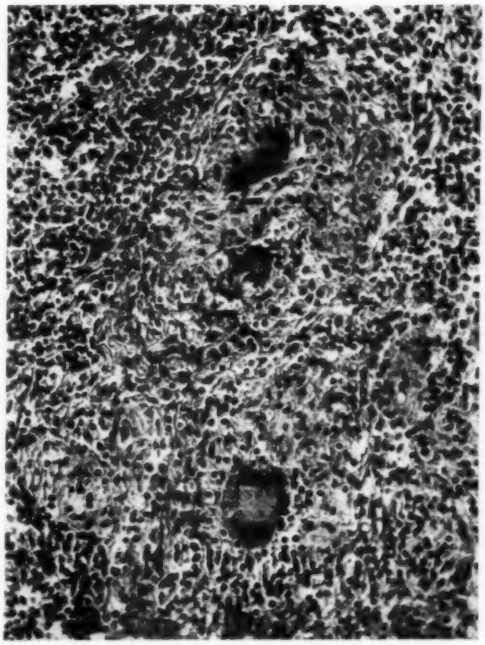

FIG. 20. CASE 4. V. G. SECTIONS OF LYMPH NODE SHOWING TUBERCLE-LIKE FORMATIONS WITH LARGE GIANT CELLS

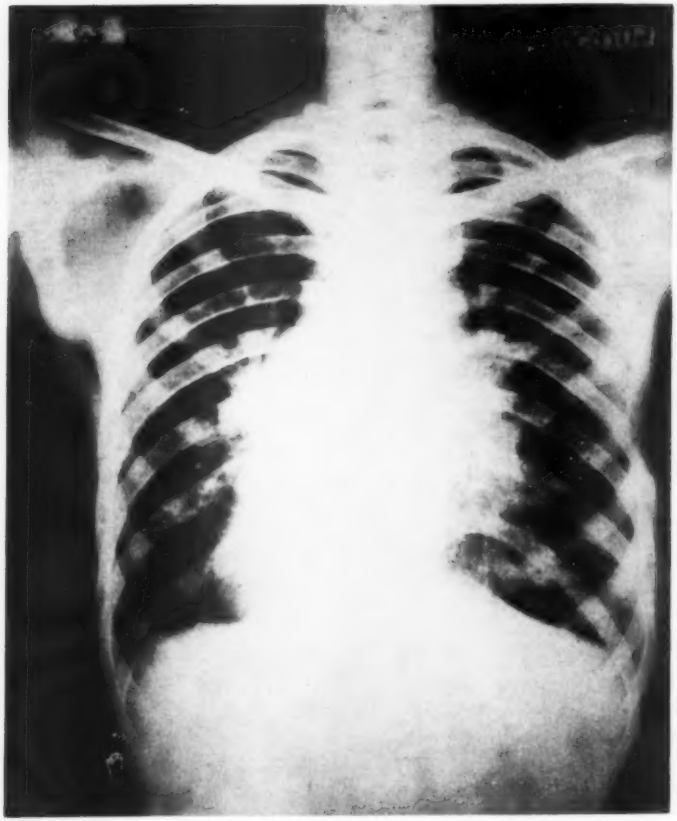

FIG. 21. CASE 5. S. H. RADIOGRAM OF CHEST SHOWING ENLARGEMENT OF BRONCHIAL LYMPH NODES AND INFILTRATION AT ROOTS OF LUNG

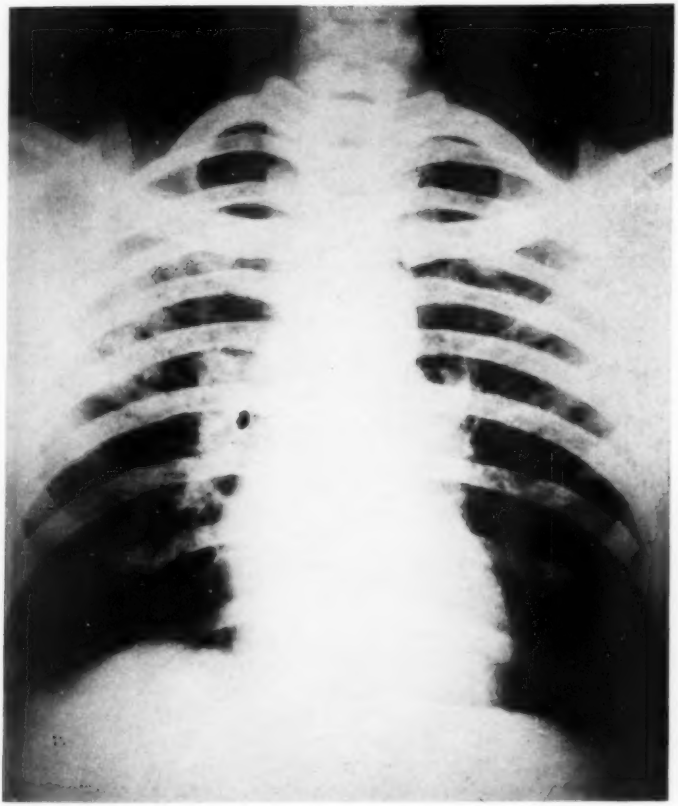

FIG. 22. CASE 6. R. K. RADIOGRAM OF CHEST SHOWING INCREASED DENSITY OF HILUS SHADOW AND IRREGULAR INFILTRATION PARTICULARLY OF RIGHT UPPER LUNG FIELD

FIG. 23. CASE 6. R. K. SECTION OF LYMPH NODE SHOWING NUMEROUS EPITHELIOID "TUBERCLE-LIKE" MASSES WITH GIANT CELLS AND CENTRAL NECROSES

FIG. 24. CASE 7. M. J. APPEARANCE OF PATIENT
Note enlargement of nose and minute nodules along eyelids

FIG. 25. CASE 7. M. J. APPEARANCE OF HANDS, SHOWING NODULAR SWELLINGS, LINEAR STRIATIONS OF NAILS AND DEFORMITIES OF TERMINAL PHALANGES

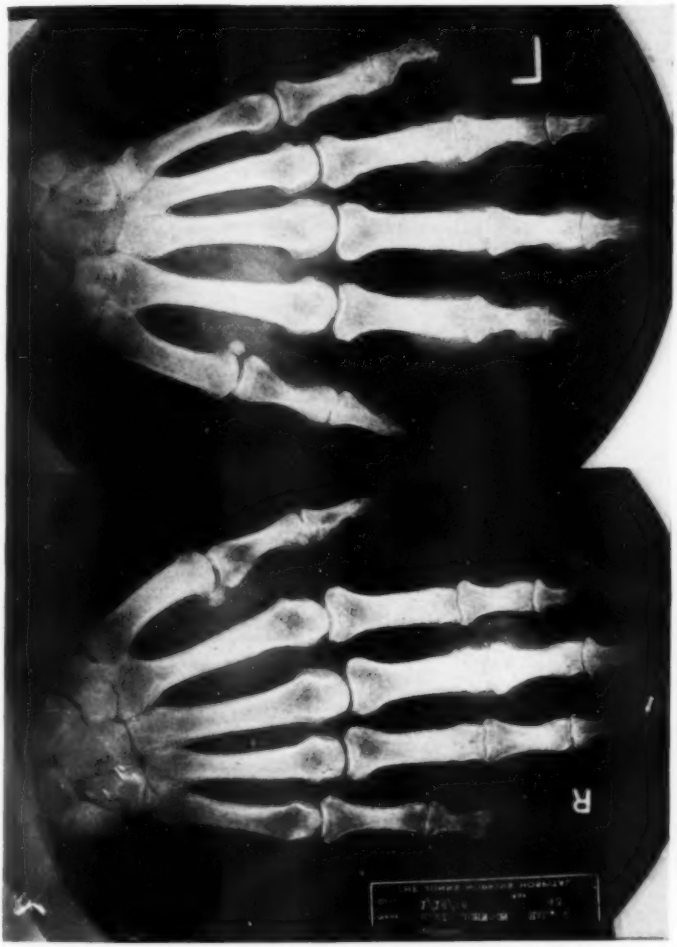

FIG. 26. CASE 7. M. J. RADIOGRAMS OF HANDS SHOWING ENLARGEMENT OF SHAFTS OF PHALANGES, MODERATE RETICULATED RAREFACTION AND SMALL ROUND PUNCHED-OUT AREA

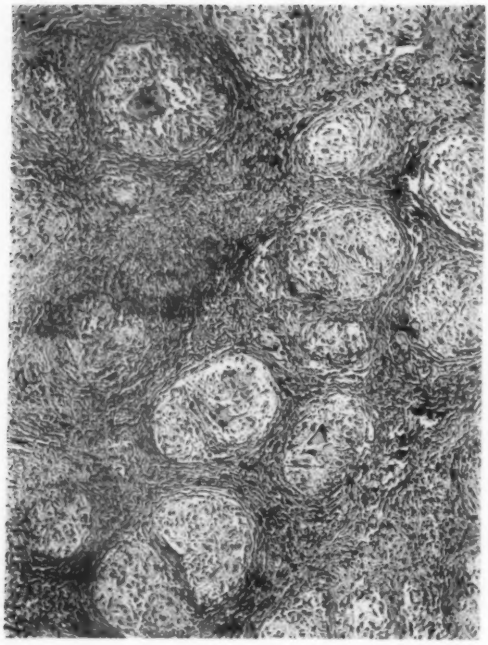

FIG. 27. CASE 7. M. J. SECTION OF NODULE FROM FINGER SHOWING CONVERSION OF EPITHELIOID "TUBERCLES" IN FIBROUS NODULES

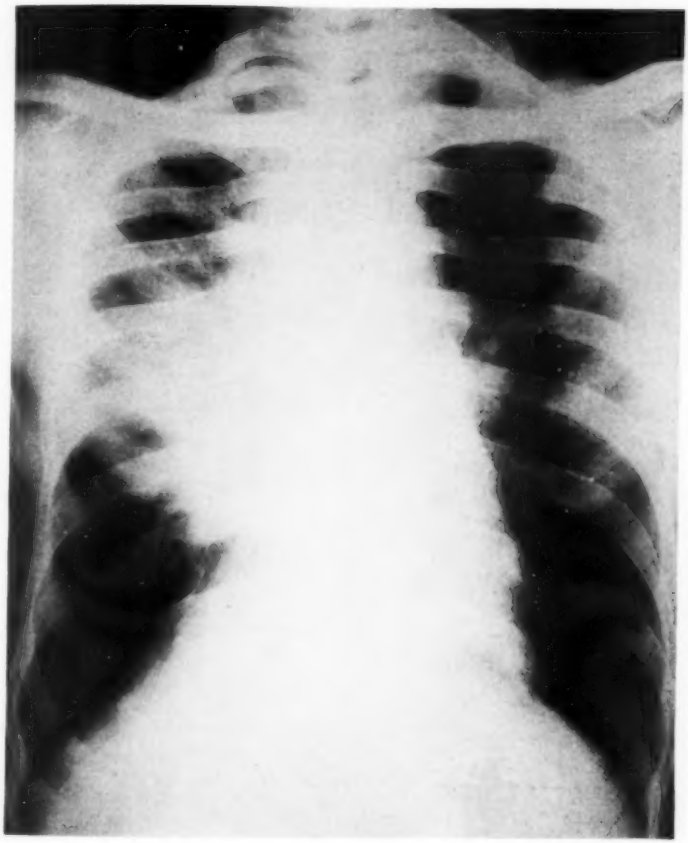

FIG. 28. CASE 8. R. H. RADIOGRAM OF CHEST SHOWING NODULAR SHADOWS AT HILUS WITH EXTENSIVE INFILTRATION FROM HILUS ON RIGHT INTO MID-LUNG FIELD

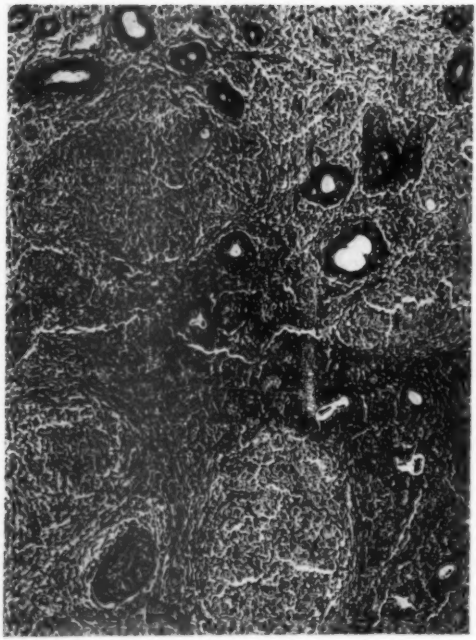

FIG. 29. CASE 8. R. H. SECTION OF PAROTID GLAND SHOWING COLLECTIONS OF EPITHELIOID CELLS IN TUBERCLE-LIKE ARRANGEMENT

THE USE OF PARA-AMINO-BENZENE-SULPHONAMIDE OR ITS DERIVATIVES IN THE TREATMENT OF BETA HAEMOLYTIC STREPTOCOCCAL MENINGITIS[1]

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Beta haemolytic streptococcal meningitis, either primary or secondary to an otitic focus, is a disease which has a very high case fatality rate. In the 37 available case records of the Johns Hopkins Hospital no recoveries from this infection have been noted in the last fifteen years. Gray (1) has reported a case fatality rate of 97 per cent in all types of streptococcal meningitis and in his admirable survey of the reported cases of recovery from streptococcal meningitis he lists but twenty-five patients ill with haemolytic streptococcal meningitis who recovered from the disease.

The recent introduction of para-amino-benzene-sulphonamide and its derivatives as specific chemotherapeutic agents in the treatment of haemolytic streptococcal infections (2, 3, 4) offers new hope of the possibility of successful therapeutic procedures in streptococcal meningitis. In this report we shall discuss the use of para-amino-benzene-sulphonamide or its derivatives in the treatment of four cases of meningitis due to haemolytic streptococci.

ABSTRACTS OF HISTORIES

Case 1. V. S., a 6-year-old white girl, was admitted to the Sydenham Hospital on December 4, 1936. Her illness began on November 25, 1936, when she developed a right earache. This lasted several days but subsided. On December 1

[1] This investigation was supported in part by a grant from the Chemical Foundation, Inc.

she became feverish, and vomited several times on this and the following day. On December 3 she began to complain of headache and was referred to the hospital by her family physician with a diagnosis of meningitis.

On admission the patient had a temperature of 104°F., pulse 120, respirations 28. She was quite intoxicated and complained constantly of headache. There was definite but moderate cervical rigidity, positive Kernig's and Brudzinski's

CHART I

Case I

DATE	SPINAL FLUID					PARA-AMINO-BENZENE-SULFONAMIDE*		REMARKS
	Cell count	Per cent P.M.N.	Globulin	Sugar	Culture	Intra-spinally	Subcu-taneously	
						cc.	cc.	
12–4	950	85	2 plus	1 plus	0			T. = 104°. 30 c.c. antimeningococcus serum. Blood culture sterile
12–5	2,250	85	2 plus	0	0			T. = 103°–105°. 15 c.c. antimeningococcus serum
12–6	3,100	90	3 plus	Trace	Positive BHS			15 c.c. antimeningococcus serum. T = 104°
12–7	3,360	80	3 plus	—	Positive BHS		200	R. mastoidectomy. Blood culture sterile
12–8	4,300	90	1 plus	Trace	0	10	200	Transfusion 140 c.c. blood
12–9	1,100	70	1 plus	1 plus	0	15	200	Transfusion 150 c.c. blood
12–10	450	80	1 plus	1 plus	0		200	Transfusion 100 c.c. blood
12–11							200	
12–12	1,250	90	1 plus	2 plus	0		200	
12–25								Discharged well

* 0.8 per cent solution in physiological salt solution.
BHS = Beta haemolytic streptococci.

signs and the right ear drum was dull and bulging. It was incised with a free flow of pus, from which Beta hemolytic streptococcus was grown on culture. There was no evidence of mastoiditis. Blood culture sterile.

Lumbar puncture yielded slightly cloudy fluid under increased pressure containing 950 cells per cu.mm. of which 85 per cent were polymorphonuclear. The Pandy test for globulin gave a ++ reaction, the qualitative Benedict's test

showed a + reaction for sugar. Since no organisms were found in a smear made from the centrifugalized sediment of the spinal fluid, 30 c.c. of antimeningococcus serum were injected intrathecally. In the following two days no organisms had grown in the culture of the spinal fluid and the patient's condition was unchanged, so that antimeningococcus serum was administered intraspinally on each of these days. On December 7, however, there were definite clinical signs of mastoiditis and it was learned that Beta hemolytic streptococcus had grown from the culture of the spinal fluid withdrawn the day before. A diagnosis of streptococcus meningitis was made.

The patient showed rapid clinical improvement following mastoidectomy and institution of treatment with para-amino-benzene-sulphonamide. Improvement continued and the drainage from the mastoid wound decreased progressively. The patient was discharged, well, on December 25, 1936, on the twenty-second hospital day (Chart I).

Case 2. R. B., a 13-year-old white boy, entered the Hartford Hospital on December 13, 1936, complaining of headache, fever and vomiting of eight days' duration. Four weeks before entry he had had mumps and two weeks before entry he had contracted an upper respiratory tract infection accompanied by constitutional manifestations. Physical examination revealed an acutely ill boy. The pharynx was inflamed; the neck and back were rigid and a definite opisthotonos was present; Kernig's sign was positive on both sides. A lumbar puncture showed that the cerebrospinal fluid was under increased pressure and contained about 2,000 polymorphonuclear leucocytes. The culture of the fluid showed Beta hemolytic streptococci. The subsequent course of this case is shown in the accompanying chart (Chart II). It is interesting to note that on the twenty-fifth day the boy developed fever and signs of an acute glomerular nephritis which cleared rapidly. The antistreptococcal serum used in the treatment of this case did not contain any demonstrable antibodies against the strain of hemolytic streptococcus isolated from the spinal fluid of the patient.

Case 3. J. C., a 9-year-old white boy, entered the Garfield Hospital on December 19, 1936, complaining of a draining right ear and headache of three days' duration. Since the age of one year he had suffered from a chronic otitis media on the right side. Physical examination showed an acutely ill boy. A thin serous discharge was visible in the right external auditory canal; definite mastoid tenderness was present on the right side; marked cervical rigidity was present; Kernig's sign was positive on both sides. A lumbar puncture was made and turbid fluid under increased pressure was obtained. A smear from the sediment showed many polymorphonuclear leucocytes and Gram-positive organisms in chains. The spinal-fluid culture showed Beta hemolytic streptococci. A simple right mastoidectomy was performed and it was found that the infection had eroded into the dura. The subsequent course of the patient is shown in Chart III. It is interesting that the recurrence of the meningeal symptoms and signs which

occurred from December 29 to January 2, while accompanied by a rise in the cerebrospinal-fluid cell count, did not result in the finding of organisms in the fluid.

CHART II

Case 2

DATE	P.A.B.S. PER OS	CEREBROSPINAL FLUID	REMARKS
	grams		
12–13–36		2000 cells BHS*	T. = 103°–104°. Antimeningococcus serum —30 c.c. Blood culture—no growth. Throat culture—BHS
12–14	4.5	5000 cells BHS	Antistreptococcal serum i.s.†
12–15	3.3	Culture negative	Transfusion—250 c.c. citrated blood. Antistreptococcal serum i.s.
12–16	1.5	BHS	Transfusion—250 c.c. citrated blood. Antistreptococcal serum i.s.
12–17	2.4	Culture negative	Transfusion—250 c.c. citrated blood
12–18	2.4		Antistreptococcal serum i.s.
12–19	2.4	Culture negative	Transfusion—250 c.c. citrated blood
12–20	2.4		Temperature essentially normal
12–21	2.4	245 cells. Culture negative	Blood culture— no growth
12–22	2.4	240 cells	Transfusion—250 c.c. citrated blood
12–23	2.4	130 cells	
12–24	2.4	88 cells	Transfusion—250 c.c. citrated blood
12–25	2.4		
12–26	2.4		
12–27 to 1– 9–37	0		Acute glomerular nephritis 12–31
1–10 to 1–24	31.2		Fever disappeared after 3 days. Urine cleared gradually
1–24 to 2– 1			Patient much improved. Up and about. Slight albuminuria. Ready for discharge

* BHS = Beta haemolytic streptococci.

† i.s. = intraspinally.

P.A.B.S. = Para-amino-benzene-sulphonamide.

Case 4. (J. H. H. No. 74475). R. E., a forty-five-year-old white male, was referred to the surgical clinic on December 8, 1936, because of signs of an intracranial tumor. The following day a ventricular air injection was made followed by a left craniotomy with removal of a dural tumor. The postoperative course

CHART III

Case 3

DATE	THERAPY			CEREBROSPINAL FLUID	REMARKS
	Intraspinally	Subcutaneously	Per os P.A.B.S.		
1936			grams		
12–19				Turbid B.H.S.	T. = 103°–104°. R. mastoidectomy
12–20				1650 cells	Transfusion 200 c.c. citrated blood. Marked cervical rigidity
12–21		P.S. 25 c.c.		1660 cells B.H.S.	Transfusion 200 c.c. citrated blood. Marked cervical rigidity
12–22	P.S. 20 c.c.	P.S. 40 c.c.		2000 cells	Temperature rose to 106.6° after *Prontosil Solution* was given intraspinally
12–23	P.A.B.S. 0.090 gram		5.4	5000 cells	Temperature fell during day to 102.2°. CO_2 = 40 vols. %
12–24	P.A.B.S. 0.090 gram		2.4	800 cells	Cervical rigidity markedly decreased. T. = 100°–101°
12–25	P.A.B.S. 0.120 gram		3.6		Marked improvement. T. = 100°–101°. CO_2 = 42 vols. %
12–26				250 cells	Marked improvement. No
12–28			4.5		cervical rigidity. T. = 99°–100°
12–29	P.A.B.S. 0.120 gram		3.0		Moderate rigidity of neck returned. Temperature became elevated to 101.4°
12–30			3.6	3400 cells	T. = 100°–101°. Rigidity of neck increased
12–31	P.A.B.S. 0.090 gram		3.6	Cultures negative	Transfusion 200 c.c. citrated blood
1937					
1–1			1.8		Moderate rigidity of neck and headache. Transfusion 250 c.c. of citrated blood. T. = 101° to 102°
1–2			3.0		Marked decrease in rigidity of neck

CHART III—*Concluded*

DATE	THERAPY			CEREBROSPINAL FLUID	REMARKS
	Intraspinally	Subcutaneously	Per os P.A.B.S.		
1937			*grams*		
1–3			2.4		T. = 99°–100°. Marked improvement
1–4			3.0		
1–5					Patient continued to improve and was discharged on January 9
1–9			15.0		

B.H.S. = Beta hemolytic streptococcus.
P.S. = *Prontosil Solution.*
P.A.B.S. = Para-amino-benzene-sulphonamide.

of the patient was uneventful until the seventh day; at this time it was noted that a wound infection with beginning cellulitis of the scalp was present. A culture of the discharge from the wound, taken at this time, showed Beta hemolytic streptococci. The patient's temperature rapidly became elevated and, on the eighth day after operation, in addition to the cellulitis, definite cervical rigidity was observed. The craniotomy wound was explored and specific chemotherapy with para-amino-benzene-sulphonamide was instituted. On the eighth day after operation (12–16–36) cultures of the cerebrospinal fluid showed Beta hemolytic streptococci. This patient's course is shown in Chart IV. Following the exploration for a brain abscess on December 26 an infected "cerebral fungus" developed together with a constant flow of cerebrospinal fluid from the left ventricle. Therapy with para-amino-benzene-sulphonamide resulted in clinical acidosis as evidenced by slight cyanosis, air hunger and a CO_2-combining power of 35.3 volumes per cent. The patient's condition became increasingly grave and he died on the fifth of January, 1937. Autopsy which was limited to examination of the head showed a sub-acute meningitis. Cultures could not be made because the brain had been embalmed before removal. Bacterial stains of the meninges showed gram-positive cocci in pairs and chains.

DISCUSSION

It is interesting to note that in this group, two of the patients had a primary otitic focus, one a traumatic focus (craniotomy wound) and in the fourth no purulent focus was discovered. In three patients surgical intervention (mastoidectomy, exploratory craniotomy) accompanied therapy with para-amino-benzene-sulphonamide or its derivatives. Three patients received intraspinal therapy with these

CHART IV

Case 4

DATE	PARA-AMINO-BENZENE-SULPHONAMIDE			CEREBROSPINAL FLUID	REMARKS*
	Intra-spinally	Subcu-taneously	Per os		
	grams	*grams*	*grams*		
12–15–36			0.6		T. = 104°. Exploration craniotomy wound. Cellulitis around wound. BHS in discharge. Marked rigidity of neck
12–16		3.2	6.0	1600 cells BHS	T. = 104°–105°. Neck rigid
12–17			4.8	Neg.	Cellulitis arrested, and healing rapidly. Neck relaxing. T. = 102°–104°
12–18	0.090		6.0	Neg.	Removal of bone flap. Transfusion. T. = 102°–104°
12–19			6.0		Transfusion. T. = 100°–102°. CO_2—40 vols. %
12–20			2.4		T. = 100.6°–102.4°
12–21					Clinical acidosis. T. = 101°–102.6°. CO_2—31.5 vols. %. 1/6 Molar sodium lactate, 300 c.c. i.v. and 300 c.c. s.c.
12–22 to 12–25					Acidosis disappeared. Temperature normal. Marked clinical improvement
12–25			1.2		BHS still present in discharge from wound. Slight elevation in temperature
12–26			4.8		Exploratory craniotomy for possible brain abscess. Accidental entry into left ventricle. T. = 103°
12–27	0.160		5.4		Clinical acidosis. CO_2—35.3 vols. %. 1/6. Molar sodium lactate, 400 c.c. i.v. and 400 c.c. s.c. T. = 104°
12–28			3.6		Acidosis. CO_2—38.4 vols. %
12–29			3.6		Acidosis. T. = 104°–105°
12–30			1.8		Acidosis. CO_2—27.7 vols. %. 1/6. Molar sodium lactate 400 c.c. i.v. and 600 c.c. s.c.
12–31					Acidosis abating. T. = 103°–104°. CO_2—43.8 vols. %
1–1–37					Condition grave. BHS in discharge from wound
1–2			2.4		T. = 103°–104°
1–3			1.2		T. = 103°–104°
1–4					T. = 103°–104°
1–5					T. = 107°. Died

* BHS = Beta haemolytic streptococci.

i.v. = intravenously.

s.c. = subcutaneously.

chemicals while, in the other patient, oral therapy alone (with para-amino-benzene-sulphonamide) was used. Three patients recovered and one died.

Although our series of cases is small, it would seem that certain practical conclusions can be drawn from it. In the first place, it appears that the use of para-amino-benzene-sulphonamide or its derivatives offers the possibility of a specific chemotherapeutic approach to the treatment of Beta haemolytic streptococcal meningitis. The best method of administration obviously can not be arrived at from the experience in this small series, but probably a combination of oral and intraspinal therapy with para-amino-benzene-sulphonamide deserves a thorough trial. The following outline, based on our experience with these four cases, provides a tentative plan for the treatment of future cases of streptococcal meningitis.

If the patient is not nauseated and can swallow, treatment should be started with para-amino-benzene-sulphonamide by mouth and also by the intraspinal route.

Para-amino-benzene-sulphonamide *tablets* are used for oral administration.[2] The total dose for the first 24 hours is calculated upon the basis of 3 tablets (1 gram) per 20 pounds of body weight up to 100 pounds of body weight. For adults with acute infections we believe that 5 grams of this substance represents the maximum daily dose that may be used with safety. This total amount is divided into four doses given at intervals of six hours. Thus, for a patient weighing 100 pounds the total amount required for the first day would be 16 tablets, or 4 tablets every 6 hours. Crystalline para-amino-benzene-sulphonamide is not generally available at the present time, nor is it entirely satisfactory for use because of certain difficulties in its administration to the patient. This chemical is soluble up to, roughly, 0.8 per cent in physiological salt solution. In preparing it for clinical use it is our practice to dissolve 0.8 gm. in 100 c.c. of physiological salt solution which has been brought to the boiling point and then cooled to about 90°C. Such 0.8 per cent solutions of para-amino-benzene-sulphonamide may be used intrathecally in the treatment of streptococcal meningitis. In general it has been the experience of those who have

[2] These tablets contain foreign material which renders them unsuitable for parenteral administration.

used para-amino-benzene-sulphonamide in this way that very little cellular reaction to the chemical has been observed and no toxic manifestations. The general practice in administering the drug intrathecally should closely follow that recommended for the use of antimeningococcus serum in meningococcal meningitis, namely, that rather complete spinal drainage by lumbar puncture should be instituted and then from 15 c.c. to 25 c.c. of a warm, freshly prepared, 0.8 per cent solution of para-amino-benzene-sulphonamide should be permitted to flow in by *gravity*. The solution should never be injected under pressure.

If the patient cannot swallow tablets, parenteral therapy by the subcutaneous route with either *Prontosil Solution* or an 0.8 per cent solution of para-amino-benzene-sulphonamide in sterile physiological salt solution may be instituted. With *Prontosil Solution* 1 c.c. per pound of body-weight constitutes the total daily dose. It has been our practice to divide this into four equal doses given at six-hour intervals. If 0.8 per cent para-amino-benzene-sulphonamide solution is used, it should be given as a hypodermoclysis in the following amounts: For patients weighing up to 40 pounds, 100 c.c. in 24 hours, 40–80 pounds, 200 c.c., 80–120 pounds, 300 c.c., and for those weighing over 120 pounds, 400 c.c. in 24 hours.

Therapy should be continued at the advised level until the spinal fluid has been rendered sterile for at least 48 hours and a marked general improvement in the patient's condition has been noted. At this point the intraspinal therapy may be discontinued and the amount of the drug given by mouth reduced by one third. It should be borne in mind that, because of possible recurrences of the infection, adequate oral therapy should be maintained until the patient is entirely well.

If crystalline para-amino-benzene-sulphonamide is not available, it is probable that the administration of the tablets by mouth (or, when oral administration is impracticable, the subcutaneous injection of *Prontosil Solution*) together with frequent spinal-fluid drainage may suffice. Our experience with the intraspinal injection of *Prontosil Solution* in one of the reported patients and in other instances of non-streptococcal meningitis leads us to the conclusion that this preparation is not very suitable for intraspinal therapy. It appears to be

definitely irritating to the meninges and frequently causes a marked cellular reaction with a distinct elevation of temperature.

In the light of our present knowledge we believe that surgical procedures designed to eradicate septic foci are indicated in streptococcal meningitis as an adjunct to specific therapy. It should, however, be remembered that these patients are poor surgical risks and, in our opinion, extensive surgical intervention should not be resorted to until the infection has been brought under control by the specific therapy.

SUMMARY

The case histories of four patients ill with Beta haemolytic streptococcal meningitis have been described. Three of these four patients recovered. All were treated with para-amino-benzene-sulphonamide or its derivatives.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Trachoma. By A. F. MacCallan, C.B.E., M.D., F.R.C.S. 226 pp. Illus. £1·1ˢ. (*Butterworth & Co., Ltd., London, 1936.*)

This 226-page volume is an amplification of the Hunterian Lecture of 1936. Mr. MacCallan is the former Director of Egyptian Government Ophthalmic Hospitals, and is now President of the International Organization Against Trachoma. A great part of his life has been spent in the study and fight against trachoma, and this volume by him has been awaited with anticipation and interest. But while it contains much valuable material, on the whole it is somewhat disappointing. The section on the clinical course and diagnosis of trachoma is excellent; it embodies the classification set forth in the author's previous papers, and reflects his vast experience and close study of the disease. The chapter on pathology is sound, clear, and is a concise presentation of the recent work on this subject. The chapter on treatment is direct and good, but gives one the impression that there has been essentially no progress made in trachoma therapy in the last quarter century, with the possible exception of the substitution of 10% copper sulphate for the crystals formerly used. The section devoted to the surgical treatment of the complications of trachoma contains little or nothing new, is not illustrated, and in places is difficult to follow.

The discussion of the various phases of the trachoma problem is poorly balanced. The question of unevenness of distribution in the same locality, of individual and racial immunity, is dismissed with little more than a sentence. The question of world distribution receives only the statement that the problem is too intricate and lengthy to discuss or even abstract, but the following twenty pages are devoted to the distribution of trachoma in the British Empire beyond the seas. The enormous amount of recent work on the etiology of trachoma is compressed into a few short pages, while a detailed and lengthy description is given of the various prophylactic measures against trachoma instituted in the schools of Egypt, and much space is devoted to brief and inadequate descriptions of the clinical picture and treatment of other forms of ophthalmia.

All in all, the book is extremely uneven. It would doubtless be of inestimable value to the Public Health officers of the British Empire, but is far from a reference book on trachoma.

A. C. W.

Textbook of Medicine. By CHARLES PHILLIPS EMERSON. 1296 pp. $8.00. (*J. B. Lippincott Co., Philadelphia, 1936.*)

This textbook presents in the author's words "several rather unique features." The approach to the various subjects is somewhat new and the arrangement of these is likewise new. The book is very complete and the clinical pictures of diseases are stressed rather than the pathological, anatomical and biochemical features—though the latter are not neglected. The references to the recent literature form a fairly complete and comprehensive bibliography. The short historical notes on the more outstanding physicians, as footnotes, add a great deal to the general information on the subject matter. One is not led into a labyrinth of confusion by endless statistics. Those recorded are succinct and generally accepted figures. Particular attention should be drawn to Parts Ten and Twenty, in which the psychoneurotic reactions are discussed. These subjects are too often neglected in textbooks of general medicine and the timely word of warning to all physicians and students is not out of place. In the section on the diseases of the kidney, the student will encounter some confusing statements and he may be perplexed by the classification of nephritis. The clinical features of chronic pyelonephritis with renal insufficiency are not described.

There are a few typographical errors but none very glaring except in the transposed sentences in the discussion of Chlorosis.

W. B. A.

On Your Guard! The Prevention and Treatment of Sex Diseases. By CARL WARREN. 160 pp. $1.00. (*Emerson Books, Inc., New York, 1937.*)

This little book grew out of a series of articles prepared by the author for the New York Daily News, and so is directed entirely to the layman. The style is simple and direct, and the author has done particularly well in the difficult task of expressing complex medical concepts in simple language without sacrifice of fundamental accuracy.

The history of the venereal diseases is briefly but adequately discussed and the prevalence of syphilis and gonorrhea and the means by which they are spread are graphically presented. The keynote of the book, however, is a plea for the universal employment of prophylaxis for the prevention of the spread of the venereal diseases, and the technics for both mechanical and chemical prophylaxis are described in detail. Finally, the author describes the signs and symptoms which should lead the exposed individual to suspect that he may have become infected, and with an urgent warning to him to avoid self-medication or drugstore treatment advises that he consult a physician at once.

The book should serve a useful purpose in promoting education of the public.

P. P.

The Physiology and Pharmacology of the Pituitary Body. By H. B. VAN DYKE. 577 pp. Illus. $4.50. (*University of Chicago Press, Chicago, 1936.*)

In this book the author has reviewed briefly in chapters devoted to different

aspects of the functions of the hypophysis a great number of papers—so many indeed that 182 pages of the book are required for the bibliography. In each chapter there is so much that is contradictory, so often it seems appropriate to end with such a sentence as "His data leave undecided the question of the specificity of the effects," that the book becomes a book of reference rather than a summary of the present state of knowledge. This is especially true since the author refrains from expressing his own opinion as to the relative value of the various studies which he quotes. But in this sense it is valuable, since it brings together in convenient form a great deal of the work of recent years from all parts of the world.

W. G. M.

Tissue Immunity. By REUBEN L. KAHN. 707 pp. Illus. $7.50. (*Charles C. Thomas, Springfield, Ill., 1936.*)

Dr. Kahn's essential thesis is that fixed tissue cells, in particular those of the skin, possess a specific affinity for antigen. This cellular reactivity, analogous to but wholly distinct from that of the humoral antibodies, he considers one of the most important defense mechanisms of the body. A large amount of original work is presented in support of this thesis, but to the present reviewer that evidence seems inadequate.

In the very first chapter, one is struck by the fact that, in the quantitative technique which underlies most of the experiments here reported, there are several points which are open to serious criticism. Skin reactions are used as a measure of immunity, despite the considerable body of evidence that skin sensitivity and immunity bear no necessary relationship. These skin tests are carried out with serial dilutions varying tenfold. The results so obtained, at best of qualitative significance, are treated quantitatively when a quantitative treatment is clearly not indicated. Even in the test tube, the maximum dilution of antigen which suffices to give a positive precipitation reaction bears no necessary relationship to the amount of antibody present. If this relationship does not hold *in vitro*, it becomes all the more questionable in so complex a phenomenon as skin reactivity. Finally, Dr. Kahn compares the agglutinating titer of an antiserum, determined by diluting the serum, with a skin reacting titer, determined by diluting an antigen. The comparison would seem to be devoid of significance. Throughout the volume, results obtained with these several methods of titration are used as evidence for the major thesis of tissue immunity, but in view of the foregoing considerations, the validity of this evidence is questionable.

It is well established that antibodies are present in the tissue fluids of immunized animals, and that these antibodies are *per se* capable of "fixing" antigen, without the necessary participation of tissue cells. In any experimental work presented as evidence for an entirely distinct localizing mechanism, due cognizance must accordingly be taken of the possible presence of antibody in the tissue fluids. Dr. Kahn's case for "tissue immunity" rests on two critical experiments. The skin develops the property of localizing antigen well before demonstrable anti-

bodies appear in the serum, and conversely, this property persists long after the serum antibodies have disappeared. This, however, does not suffice to prove that the tissue cells cause that fixation in the absence of antibody. Others have clearly shown that agglutination occurs *in vivo* in the absence of antibody demonstrable *in vitro*. Certainly the possibility must be considered that any antigen introduced into the skin can call on the entire organism's store of antibody, while in the test tube reaction one uses at most 1 or 2 cc. of serum. As is true repeatedly in this volume, highly pertinent antecedent work is here ignored.

In the second place, the mere fact that the skin is several times as active in fixing antigen in the immunized animal as are other tissues hardly suffices to prove a specific reactivity of the fixed cells of the skin. There are too many uncontrolled variables, such as the rate of absorption from the various tissues of the normal animal, or the amount of interstitial fluid relative to cellular tissue in the several organs, to make that argument immediately valid.

On rather insufficient grounds, revolutionary concepts are given considerable prominence. The statement is made that inflammation and necrosis in skin reactions are not causally related, but that necrosis is caused by the influx of antigen from the blood stream into an already specifically inflamed focus. Granted that under certain experimental conditions, necrosis can be so induced, the generalization that, *e.g.*, the necrosis of a chancre and tuberculous caseation are similar phenomena, seems wholly unwarranted. Anyone who has seen a dark field preparation of an acutely inflamed rabbit chancre swarming with spirochetes will seriously question the thesis that the subsequent necrosis is due to the deposition of a few more spirochetes from the circulating blood. Nor can one accept without further evidence the statement that tuberculous caseation is a similar necrosis caused by the introduction of tubercle bacilli from the blood into a specifically inflamed focus.

The classification of the several types of immune states is open to criticism on several grounds, not the least of which is the use of new terms, such as "disimmunization," for well recognized phenomena.

H. E.

The Life and Convictions of William Sydney Thayer, Physician. By Edith Gittings Reid. 243 pp. Illus. $2.50. (*Oxford University Press, London, New York, Toronto, 1936.*)

This account of the career of Thayer by a lay friend, who had known him intimately for years, will be welcomed by his numerous admirers in and outside the medical profession. The volume is delightfully written and gives the outstanding events in his career, from his entry to Harvard at sixteen to his sudden death on December 10th, 1932, at sixty-eight years of age. The author emphasizes Thayer's intellectual background. His father for many years was a professor at Harvard and was a recognized authority on Constitutional Law. His youngest brother, Ezra, became Dean of the Harvard Law School. His maternal grandmother was Sara Alden Ripley, whose nephew was Ralph Waldo Emerson, and who was a proficient Greek and Latin scholar as well as a master

of the modern languages. From her Thayer probably inherited his great facility in learning to speak French, German and Russian.

Although the author portrays Thayer's ability and influence as a great clinician, diagnostician, and teacher, yet a medical man, in writing his life, would no doubt have emphasized to a greater extent one of his numerous influences on medical education in this country by the establishment, through Osler's suggestion, of a course in Clinical Microscopy at the Johns Hopkins Medical School for the examination of the blood and of body secretions and excretions. This example was followed by the introduction of similar courses in many other medical schools in this country. Greater emphasis would probably also have been placed on his noteworthy work on his study of the malarial parasites and the dissemination of our knowledge of malarial infections, as well as on his splendid contribution to our information concerning bacterial endocarditis.

The author, however, gives an excellent portrayal of Thayer's personality—his little foibles of dress, constant wearing of a carnation, acknowledged lack of executive ability owing to his greater interest in the problems of disease, Nimrod propensities in his later years, and his quite considerable talent as a poet and also as a translator of Russian poems. Few of his friends were aware that he had kept a very complete diary and also that for fifteen years after the death of Mrs. Thayer on September 3rd, 1917, while he was in Russia, he wrote to her daily in his diary. This diary is freely quoted. From this source one gets a vivid account of his experiences in Russia during the Revolution, when he was a member of the American Red Cross Mission to Russia in 1917, during which time his life was often imperilled while he was detailed in the city of Moscow. From the same source, also, the author portrays vividly Thayer's experiences in France in 1918, when he was Chief Consultant of Medical Services in the American Expeditionary Force.

Those familiar with the history of the earlier years of the Johns Hopkins Hospital will be struck by some inaccuracies on the part of the author. On page 43 the assertion is made "During the winter of 1891 Osler was busy writing his *Practice of Medicine*, Lazear and Thayer relieving him of his ward work." The fact is that Lazear was not on the hospital staff until years later, his service being from August, 1895, to June, 1896. The statement on the same page is also made that after Osler was married (which was in May, 1892) the Oslers took possession of their house at 1 W. Franklin Street and that "a group of his assistants, Thayer among them, promptly moved into the adjacent house" and were called the 'latch-keyers.' As a matter of fact, Thayer continued to live at the Johns Hopkins Hospital as Resident Physician until September 1st, 1898, when he joined Dr. H. B. Jacobs at 3 West Franklin Street,

These and a few other minor inaccuracies do not materially detract from this most interesting portrayal of the life of Thayer, who was probably the outstanding clinician and diagnostician in this country at the time of his death. His innumerable friends and former medical students will find the volume most entertaining and instructive.

T. B. F.

BOOKS RECEIVED

The Truth about Bright's Disease. By WILLIAM R. OHLER. 80 pp. $1.00. Harvard University Press, Cambridge, Mass., 1936.

The Physiology and Pharmacology of the Pituitary Body. By H. B. VAN DYKE. 577 pp. Illus. $4.50. University of Chicago Press, Chicago, 1936.

Convalescent Care in Great Britain. By ELIZABETH GREENE GARDINER. 163 pp. $1.50. University of Chicago Press, Chicago, 1935.

Greek Medicine. By FRED B. LUND. [Clio Medica xviii.] 161 pp. $2.00. Paul B. Hoeber, New York, 1936.

Life and Convictions of William Sydney Thayer, Physician. By EDITH GITTINGS REID. 243 pp. Illus. $2.50. Oxford University Press, New York, 1936.

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On Your Guard! The Prevention and Treatment of Sex Diseases. By CARL WARREN. 160 pp. $1.00. Emerson Books, Inc., New York, 1937.

Into this Universe. The Story of Human Birth. By ALAN FRANK GUTTMACHER. 366 pp. Illus. $2.75. Viking Press, New York, 1937.

Psychiatry for Practitioners. By various authors. Edited by HENRY A. CHRISTIAN. [Reprinted from Oxford Loose-Leaf Medicine.] 646 pp. $6.50. Oxford University Press, New York, 1936.

Contraception as a Therapeutic Measure. By BESSIE L. MOSES. 106 pp. $1.00. Williams & Wilkins Company, Baltimore, 1936.

Operative Surgery. By ALEXANDER MILES and D. P. D. WILKIE. 2nd ed. 631 pp. Illus. Oxford Medical Publications. Oxford University Press, London: Humphrey Milford, 1936.

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The Lung. By WILLIAM SNOW MILLER. 209 pp. Illus. $7.50. Charles C. Thomas, Springfield, Ill. & Baltimore, Md., 1937.

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An Introduction to Comparative Biochemistry. By ERNEST BALDWIN. 112 pp. $1.50. Cambridge: at The University Press. New York: The Macmillan Company, 1937.

Ultra-sons et Biologie. By A. DOGNON ET E. ET H. BIANCANI. 80 pp. Illus. Unbound, 25 fr. Gauthier-Villars, Paris, 1937.